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(71) Applicant: INSITE VISION INCORPORATED [US/US]; 965 Atlantic Avenue, Alameda, CA 94501 (US).

(72) Inventors: TSAO, Sheng-Wan; 37 Alley 648, Lane 102, Min-hu Road, Hsing-Chu 300 (TW). BOWMAN, Lyle, M.; 5135 Mt. Tam Circle, Pleasanton, CA 94566 (US).

(74) Agents: FREED, Joel., M. et al.; Howrey & Simon, 1299 Pennsylvania Avenue, N.W., Washington, DC 20004 (US).

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(54) Title: CYCLODEXTRIN AND POLYMER BASED DRUG DELIVERY SYSTEM

(57) Abstract

Pharmaceutical compositions comprising a therapeutic agent, an effective stabilizing amount of carboxy-containing polymer and cyclodextrin, in an aqueous medium, wherein said cyclodextrin is selected from the group consisting of the hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α, β and γ-cyclodextrin, modified or unmodified; and methods for stabilizing and solubilizing a therapeutic agent in a pharmaceutial composition, comprising combining said therapeutic agent in an aqueous medium with an effective stabilizing amount of carboxy-containing polymer and an amount of cyclodextrin sufficient to at least partially solubilize said therapeutic agent, said cyclodextrin being selected from the group consisting of the hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α, β and γ-cyclodextrin, modified or unmodified.

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CYCLODEXTRIN AND POLYMER BASED DRUG DELIVERY SYSTEM

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations comprising cyclodextrin or cyclodextrin derivatives, carboxy-containing polymers and therapeutic agents. The invention further relates to topical ophthalmic compositions comprising therapeutic agents, particularly, amino-substituted steroid therapeutic agents, lightly cross-linked carboxy-containing polymers and selected cyclodextrin derivatives. The invention further relates to methods of stabilizing and solubilizing amino-substituted steroid therapeutic agents in formulations using cyclodextrin derivatives, in combination with carboxy-containing polymers.

BACKGROUND

Some valuable therapeutic agents (drugs) are difficult to use because of their low stability in water or body fluids. Some therapeutic agents suffer from stability problems and they can cause irritation. Drug instability can limit the usefulness of pharmaceutical compositions containing them by shortening the shelf-life of the formulations and/or requiring stringent control of storage conditions. The insolubility of some therapeutic agents can seriously hamper efforts to utilize the compounds to their full potential because low solubility limits their bioavailability. Some aminosteroids illustrate these problems because they tend to be unstable and to have low solubility in aqueous environments such as body fluids. Instability of aminosteroids occurs primarily as a consequence of their antioxidative properties. Because they are potent antioxidants, the aminosteroids are especially sensitive to oxidative degradation. Moreover, these compounds are

subject to hydrolytic degradation and rearrangement. There is thus a need for improved pharmaceutical compositions comprising therapeutic drugs with agents that stabilize and solubilize the pharmaceutical compositions and ameliorate irritation. Providing compositions that deliver the therapeutic agent to a target site over a prolonged period of time is also an objective for many applications.

A number of publications are available pertaining to drug delivery systems, cyclodextrin, and drugs combined with cyclodextrin or pharmaceutical vehicles. It has not been suggested, however, that cyclodextrins and carboxy-containing polymers would, when combined, stabilize and solubilize therapeutic agents and be compatible with one another. It was also not known that aminosteroids disclosed in International Publication No. WO 87/01706 and U.S. Patent No. 5,124,154 (discussed below) would be compatible or stable with the combination of carboxy-containing polymers with cyclodextrins. Publications pertinent to the background of the present invention are identified below.

A variety of compositions have been formulated to deliver drugs to the eye, skin and other parts of the body in a sustained manner. Sustained release ophthalmic formulations of an ophthalmic drug and a high molecular weight polymer to form a highly viscous gel, for instance, have been described in Schoenwald et al U.S. Patent No. 4,271,143, issued June 2, 1981 and Schoenwald et al U.S. Patent No. 4,407,792, issued October 4, 1983.

U.K. Patent Application GB 2007091 A, published May 16, 1979, describes an ophthalmic composition in the form of a gel comprising an aqueous solution of a carboxyvinyl polymer, a water-soluble basic substance and an ophthalmic drug, the gel having a pH of 5 to 8 and a viscosity of 1,000 centipoises to 100,000 centipoises at 20°C.

U.K. Patent Application GB 2013084 A, published August 8, 1979, describes an aqueous gel for application to the conjunctival sac of the eye comprising an ophthalmic drug and a polymer having carboxylic or anhydride functional groups and a molecular weight in excess of 1,000,000, such as carboxypolymethylene, carboxyvinyl and ethylene maleic anhydride polymers.

Robinson U.S. Patent No. 4,615,697, issued October 7, 1986, discloses a controlled release composition and method of use based on a bioadhesive and a treating agent, such as an anti-inflammatory agent. The bioadhesive is a water-swellable, but water-insoluble, fibrous, cross-linked carboxy-functional polymer having a plurality of repeating units of which about 80 percent contain at least one carboxyl functionality and a cross-linking agent which is substantially free from polyalkenyl polyethers.

U.S. Patent No. 5,192,535, issued March 9, 1993 and assigned to the assignee hereof, describes formulation of lightly cross-linked polymers, preferably ones prepared by suspension or emulsion polymerizing at least about 90% by weight of a carboxyl-containing monoethylenically unsaturated monomer such as acrylic acid with from about 0.1% to about 5% by weight of a polyfunctional, and preferably difunctional, cross-linking agent such as divinyl glycol (3,4-dihydroxy-1,5-hexadiene), having a particle size of not more than about 50 μm in equivalent spherical diameter, with an ophthalmic medicament, e.g., the steroid fluorometholone, into suspensions in aqueous medium in which the amount of polymer ranges from about 0.1% to about 6.5% by weight, based on the total weight of the aqueous suspension, the pH is from about 3.0 to about 6.5, and the osmotic pressure (osmolality or tonicity) is from about 10 mOsM to about 400 mOsM. These new topical ophthalmic medicament delivery systems have suitably low viscosities which permit them to be easily administered to the eye in drop form, and hence to be comfortably administered in consistent, accurate dosages. These

suspensions will rapidly gel in the eye after coming into contact with the eye's tear fluid to a substantially greater viscosity than that of the originally-introduced suspension and thus remain in place for prolonged periods of time to provide sustained release of the ophthalmic medicament. See International Publication Number WO 92/00044 published January 9, 1992 and International Publication No. WO 89/06964, published August 10, 1989.

International Publication No. WO 87/01706, published March 26, 1987, which discloses a number of aminosteroids and their therapeutic use in a variety of contexts, as well as administration techniques and dosages, does not disclose treatment or prevention of ophthalmic diseases or disorders. Nor does it disclose topical application to the eye or administration by intraocular injection.

Applicants' U.S. Patent No. 5,124,154, discloses methods and compositions which are designed to enhance the ability of the tissues of the eye to respond to trauma, to aging, to surgery, to the threat of glaucoma by increasing intraocular pressure, to the potential loss of vision from progression of macular degeneration and the like by supplementing, both acutely and chronically, the natural ability of the eye to resist oxidative damage. In one aspect, the '154 invention discloses methods and compositions for preventing or treating ophthalmic diseases or disorders in a human or other animal that is subject to intraocular damage (particularly oxidative intraocular damage) and in need of improved visual function or prevention of its loss from such damage, with an ophthalmically effective amount of certain amino-substituted steroids which function as a therapeutic agent (particularly an antioxidant agent) is in an inert vehicle, to arrest processes (particularly oxidation processes) damaging to the eye.

Applicants' U.S. Patent No. 5,124,154 further relates to formulations of aminosteroids with an appropriate inert vehicle or carrier for prevention or treatment of ophthalmic diseases or disorders. Topical, intraocular and systemic routes of administration are described. The term "inert vehicle" is broadly used in those earlier applications to optionally include adjuvants, preservatives, buffers, demulcents and anything else that is essentially inert relative to the therapeutic function (particularly the antioxidant function) of the aminosteroids as that function relates to eye tissue. Topical formulations should generally include between 0.01 and 10% by weight, preferably between 0.1 and 5% by weight, of the amino-substituted steroid therapeutic agent in a suitable polymeric carrier. Polymeric carriers include lightly cross-linked carboxy-containing polymers (such as polycarbophil), dextran, cellulose derivatives, polyethyleneglycol 400 and other polymeric demulcents. Other additions taught as desirably included in the topical formulations include sodium chloride, EDTA (disodium edetate), surfactants, and preservatives such as BAK (benzalkonium chloride).

Cyclodextrins are cyclic oligosaccharides. The most common cyclodextrins are α-cyclodextrin, which is composed of a ring of six glucose residues; β-cyclodextrin, which is composed of a ring of seven glucose residues; and γ-cyclodextrin, which is composed of a ring of eight glucose units. The inside cavity of a cyclodextrin is lipophilic, while the outside of the cyclodextrin is hydrophilic; this combination of properties has led to widespread study of the natural cyclodextrins, particularly in connection with pharmaceuticals, and many inclusion complexes with drugs have been reported. β-Cyclodextrin has been of special interest because of its cavity size, but its relatively low aqueous solubility (about 1.8% w/v at 25°C) and attendant nephrotoxicity have limited its use in the pharmaceutical field.

Attempts to modify properties of the natural cyclodextrins have resulted in the development of heptakis (2,6-di-O-methyl)-β-cyclodextrin, heptakis (2,3,6-tri-O-methyl)-β-cyclodextrin, hydroxypropyl-β-cyclodextrin, β-cyclodextrin-epichlorohydrin polymer and others. For a comprehensive review of cyclodextrins and their use in pharmaceutical research, see Pitha et al, in Controlled Drug Delivery, ed. S.D. Bruck, Vol. I, CRC Press, Boca Raton, Florida, 125-148 (1983). For an even more recent overview, see Uekama et al, in CRC Critical Reviews in Therapeutic Drug Carrier Systems, Vol. 3 (1), 1-40 (1987); Uekama, in Topics in Pharmaceutical Sciences 1987, eds. D.D. Breimer and P. Speiser, Elsevier Science Publishers B.V. (Biomedical Division), 1987, 181-194; and Pagington, Chemistry in Britain, May 1987, 455-458.

Inclusion complexes of α-, β- or γ-cyclodextrin or their mixtures with a variety of drugs have been described by numerous parties and various advantages have been attributed to the complexes. These descriptions include those documents summarized in Bodor U.S. Patents Nos. 4,983,586 and 5,024,998, incorporated by reference herein in their entireties and relied upon. Particular reference may be made to Lipari U.S. Patent No. 4,383,992, which describes inclusion complexes of β-cyclodextrin itself with a variety of steroidal hormones (corticosteroids, androgens, anabolic steroids, estrogens and progestagens). The complexes are said to have improved water solubility and increased therapeutic response in the eye. However, as noted above, β-cyclodextrin has low aqueous solubility (about 1.8% w/v at 25°) with attendant nephrotoxicity.

Hydroxypropyl-β-cyclodextrin and its preparation by propylene oxide addition to β-cyclodextrin were described in Gramera et al U.S. Patent No. 3,459,731 over 20 years ago. (Gramera et al also described the analogous preparation of hydroxyethyl-β-cyclodextrin by ethylene oxide reaction with β-

cyclodextrin.) Much more recently, Pitha and co-workers have described the improved preparation of this cyclodextrin derivative and its effects on the dissolution of various drug molecules. Pitha U.S. Patent No. 4,596,795, dated June 24, 1986, describes inclusion complexes of sex hormones, particularly testosterone, progesterone and estradiol, with specific cyclodextrins, preferably hydroxypropyl-β-cyclodextrin and poly-β-cyclodextrin. The complexes enable the sex hormones to be successfully delivered to the systemic circulation via the sublingual or buccal route; the effectiveness of this delivery is believed to be due to "the high dissolution power of hydrophilic derivatives of cyclodextrins, the non-aggregated structure of their complexes with steroids, and their low toxicity and irritancy of mouth tissue". Success with other cyclodextrins, including poly-γ-cyclodextrin and hydroxypropyl-γ-cyclodextrin, have also been noted in the Pitha patent. See also Pitha et al, J. Pharm. Sci., Vol. 74, No. 9, September 1985, 987-990, concerning the same and related studies. Pitha et al also describe in the J. Pharm. Sci. publication the storage stability of tablets containing a testosterone/hydroxypropyl-β-cyclodextrin complex and the lack of toxicity of the cyclodextrin derivative itself, as well as the importance of the amorphous nature of the cyclodextrin derivatives and their complexes with drugs in improving dissolution properties.

The improved, optimized preparation and purification of hydroxypropyl-β-cyclodextrin has been described by Pitha et al, International Journal of Pharmaceutics, 29, 73-82 (1986). In the same publication, the authors have described increased water solubility for 32 drugs in concentrated (40 to 50%) aqueous solutions of hydroxypropyl-β-cyclodextrin; among the drugs for which the authors have reported improved solubilization are dexamethasone, estradiol, estriol, ethinylestradiol-3-methyl ether, ethisterone, 17-methyltestosterone norethindrone, progesterone, spironolactone and testosterone. The authors indicated this to be an extension of their earlier

work with hydroxypropyl-β-cyclodextrin, which was previously found effective for oral administration of the sex hormones to humans. Their later work reported in Pitha et al, International Journal of Pharmaceutics, 29, 73-82 (1986), has also been described in Pitha U.S. Patent No. 4,727,064, dated February 23, 1988. That patent claims a composition containing an amorphous complex of cyclodextrin and a drug, and a method of producing a stabilizing amorphous complex of a drug and a mixture of cyclodextrins comprising (1) dissolving an intrinsically amorphous mixture of cyclodextrin derivatives which are water soluble and capable of forming inclusion complexes with drugs in water; and (2) solubilizing lipophilic drugs into aqueous media to form a solution and form a solubilized drug/cyclodextrin complex. The patent describes the preparation of various substituted amorphous cyclodextrins, including hydroxypropyl-β-cyclodextrin and hydroxypropyl-γ-cyclodextrin, the latter by analogous condensation of propylene oxide and γ-cyclodextrin.

Uekama et al, CRC Critical Reviews in Therapeutic Drug Carrier Systems, Vol. 3 (1), 1-40 (1987), have described the characteristics of various cyclodextrins, including hydroxypropyl-β-cyclodextrin. The authors have presented data showing improved solubilization in water in the presence of 15 mg/mL of hydroxypropyl-β-cyclodextrin for the drugs carmofur, diazepam, digitoxin, digoxin, flurbiprofen, indomethacin, isosorbide dinitrate, phenytoin, prednisolone, progesterone and testosterone. Uekama et al have indicated that cyclodextrins at sufficiently high concentrations cause hemolysis, and that the methylated cyclodextrins have higher hemolytic activity than the natural cyclodextrins. Hydroxypropyl-β-cyclodextrin is said to cause hemolysis beginning at 4.5 mM. The authors have further indicated that parenteral administration of large doses of cyclodextrins should be avoided, but that "γ-cyclodextrin and hydroxypropyl-β-cyclodextrin seem to be useful in drug

solubilization for injections and liquid preparations used for mucous membranes."

JANSSEN PHARMACEUTICA N.V.'s International Patent Application No. PCT/EP84/00417, published under International Publication No. WO85/02767 on July 4, 1985, has described pharmaceutical compositions comprising inclusion compounds of drugs, which are unstable or only sparingly soluble in water, with partially etherified β-cyclodextrin derivatives having hydroxyalkyl and optionally additional alkyl groups. Among the cyclodextrin derivatives contemplated is hydroxypropyl-β-cyclodextrin, while the drugs include nonsteroidal anti-rheumatic agents, steroids, cardiac glycosides and derivatives of benzodiazepine, benzimidazole, piperidine, piperazine, imidazole and triazole. Pharmaceutical compositions described in WO 85/02767 include oral, parenteral and topical formulations, with 4 to 10% solutions of cyclodextrin derivatives being used to solubilize various drugs. Improved solubilities of indomethacin, digitoxin, progesterone, dexamethasone, hydrocortisone and diazepam using 10% hydroxypropyl-β-cyclodextrin are reported.

The preparation of amorphous water-soluble cyclodextrin derivatives, including 2-hydroxyethyl-β-cyclodextrin, 3-hydroxypropyl-β-cyclodextrin and 2-hydroxypropyl-γ-cyclodextrin, is described by Irie et al, Pharmaceutical Research, Vol. 5, No. 11, 1988, 713-717. That report also addresses the distribution of the substituents among the glucose residues of the cyclodextrin ring.

A pharmaceutical evaluation of hydroxyalkyl ethers of β-cyclodextrin has been reported by Yoshida et al, International Journal of Pharmaceutics 46, 1988, 217-222. Aqueous solubilities, surface activities, hemolytic activity and local irritancy are reported. The data suggest that hydroxyalkyl-β-

cyclodextrins overcome many of the undesirable characteristics of β-cyclodextrin usage in pharmaceuticals.

JANSSEN PHARMACEUTICA N.V.'s European Patent Application No. 86200334.0, published under EPO Publication No. 0197571 on October 15, 1986, describes γ-cyclodextrin derivatives which are γ-cyclodextrin substituted with C_1-C_6 alkyl, hydroxy C_1-C_6 alkyl, carboxy C_1-C_6 alkyl or C_1-C_6 alkyloxycarbonyl C_1-C_6 alkyl or mixed ethers thereof. Among the specific derivatives named are hydroxypropyl-γ-cyclodextrin and hydroxyethyl-γ-cyclodextrin. Compositions comprising the cyclodextrin derivatives and a drug are also described. See also corresponding Müller United States Patent No. 4,764,604, dated August 16, 1988.

Uekama, in Topics in Pharmaceutical Sciences 1987, eds. D.D. Breimer and P. Speiser, Elsevier Science Publishers B.V. (Biomedical Division), 1987, 181-194, has described the effects on bio-pharmaceutical properties of maltosyl and glucosyl cyclodextrin derivatives, as well as hydroxypropyl and other hydrophilic cyclodextrin derivatives, including enhanced drug absorption. The mechanism of enhancing drug absorption is described and the apparent stability constants for inclusion complexes of various drugs with β-cyclodextrin, dimethyl-β-cyclodextrin, hydropropyl-β-cyclodextrin and maltosyl-β-cyclodextrin are given. Drugs studied with these cyclodextrins include prednisolone, progesterone, spironolactone and testosterone.

Koizumi et al, Chem. Pharm. Bull. 35 (8), 3413-3418 (1987), have reported on inclusion complexes of poorly water-soluble drugs with glucosyl cyclodextrins, namely 6-O-α-D-glucosyl-α-CD (G_1-α-CD), 6-O-α-D-glucosyl-β-CD (G_1-β-CD) and 6A, 6^D-di-O-α-D-glucosyl-β-CD ($2G_1$-β-CD).

Okada et al, Chem. Pharm. Bull. 36(6), 2176-2185 (1988), have reported on the inclusion complexes of poorly water-soluble drugs with maltosyl cyclodextrins, namely 6-O-α-maltosyl-α-CD (G_2-α-CD), 6-O-α-maltosyl-β-CD (G_2-β-CD), 6-O-α-maltosyl-γ-CD (G_2-γ-CD), 6-O-α-maltotriosyl-α-CD (G_3-α-CD), 6-O-α-maltotriosyl-β-CD (G_3-β-CD) and 6-O-α-maltotriosyl-γ-CD (G_3-γ-CD).

Yamamoto et al, in International Journal of Pharmaceutics 49, 163-171 (1989), have described physicochemical properties of branched β-cyclodextrins such as glucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin and dimaltosyl-β-cyclodextrin, and their inclusion characteristics. Those authors report that the branched β-cyclodextrins are better solubilizers for poorly water-soluble drugs and have less hemolytic activity than β-cyclodextrin itself, and they suggest that glucosyl-β-cyclodextrin and maltosyl-β-cyclodextrin may be especially useful in parenteral preparations.

Japanese Kokai 63-135402 (TOKUYAMA SODA KK), published June 7, 1988, describes compositions consisting of maltosyl-β-cyclodextrin and at least one of digitoxin, nifedipine, flurubiprophene, isosorbide nitrate, phenytoin, progesterone or testosterone. The compositions have improved water solubility and reduced erythrocyte destruction, are safe for humans and can be used as injections, eye drops, syrups, and for topical and mucous membrane application.

Japanese Kokai 62-281855 (DAIKIN KOGYO KK), published December 7, 1987, describes stable, water-soluble inclusion compounds of maltosyl-β-cyclodextrin with a variety of vitamins and hormones, e.g. steroid hormones such as prednisolone, hydrocortisone and estriol. These lipophilic vitamins and hormones can thus be used as aqueous solutions.

Japanese Kokai 63-036793 (NIKKEN CHEM KK), published February 17, 1988, describes the preparation of dimaltosyl-γ-cyclodextrin and its general use in medicines.

Japanese Kokai 62-106901 (NIKKEN CHEM KK), published May 18, 1987, describes the preparation of diglucosyl-β-cyclodextrin and its general use for pharmaceuticals.

Japanese Kokai 61-236802 (NIKKEN CHEM KK), published October 22, 1986, describes the preparation of maltosyl-γ-cyclodextrin and its general use with drugs.

Japanese Kokai 61-197602 (NIKKEN CHEM KK), published September 1, 1986, describes the preparation of maltosyl-β-cyclodextrin and its expected use in medicines.

Japanese Kokai 61-070996 (NIKKEN CHEM KK), published April 11, 1986, describes the preparation of maltosyl-α-cyclodextrin and its general use in pharmaceuticals.

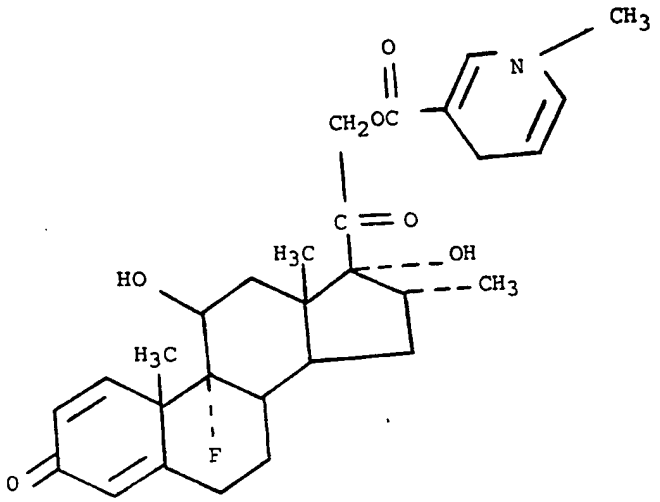
Japanese Kokai 63-027440 (SANRAKU OCEAN), published February 5, 1988, describes compositions containing a water-insoluble or slightly soluble drug together with glucosylated branched cyclodextrin. Among the drugs mentioned are steroid hormones.

Japanese Kokai 62-164701 (SHOKUHIN SANGYO BIO), published July 21, 1987, describes the preparation of diglucosyl-α-cyclodextrin and its general use in medicine.

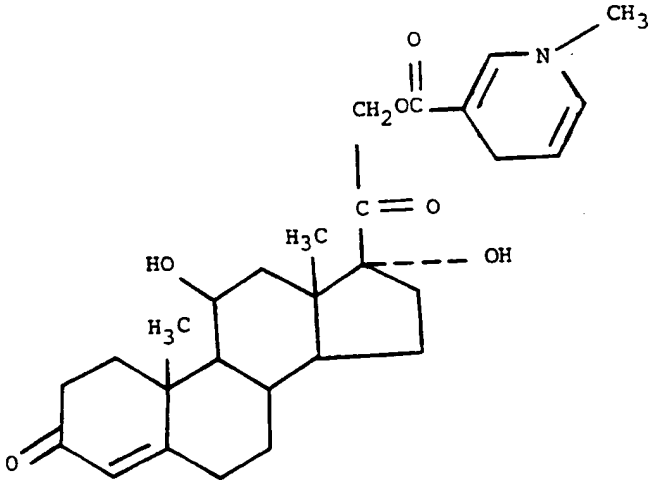
Japanese Kokai 62-003795 (TOKUYAMA SODA KK), published January 9, 1987, describes production of glucose and maltoligosaccharide (2-4 glucose units) derivatives of α-, β- and γ-cyclodextrin and their use as stabilizers for pharmaceuticals.

Bodor U.S. Patents Nos. 5,002,935, issued March 26, 1991, and 5,017,566, issued May 21, 1991, relate to stabilizing the reduced, dihydropyridine forms of dihydropyridine ⇌ pyridinium salt redox systems for brain-targeted drug delivery by complexation with cyclodextrin selected from the group consisting of hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of β- and γ-cyclodextrins. The complexes also provide a means for increasing the ratio of initial brain to lung concentrations of drug, leading to decreased toxicity. In selected instances, improved water solubilities are noted as well. In a preferred aspect, the redox system is a redox carrier system and the reduced, dihydropyridine form can be represented by the formula [D-DHC] wherein [D] is a centrally acting drug species and [DHC] is the reduced, biooxidizable, blood-brain barrier penetrating, lipoidal form of a dihydropyridine ⇌ pyridinium salt redox carrier. The "centrally acting" drug species is broadly defined and includes many classes of drugs, including steroids and, specifically, anti-inflammatory adrenal cortical steroids such as hydrocortisone, betamethesone, cortisone, dexamethasone, flumethasone, fluprednisolone, meprednisone, methyl prednisolone, prednisolone, prednisone, triamicinolone, cortodoxone, fludrocortisone, flurandrenolone acetonide (flurandrenolide), paramethasone and the like. The "dihydropyridine carrier" or "[DHC]" is defined as any nontoxic carrier moiety comprising, containing or including the dihydropyridine nucleus, the only criterion being capacity for BBB penetration and in vivo oxidation to the corresponding quaternary pyridium salt. Among the specific redox carrier drugs for complexation with cyclodextrins in accord

with the Bodor patents are a number of steroid derivatives, including the derivatives of dexamethasone and hydrocortisone shown below:



9-flouro-11β, 17-dihydroxy-16α-methyl-21-{[(1-methyl-1,4-dihydropyridin-3-yl)carbonyl]oxy}pregna-1,4-diene-3,20-dione (dexamethasone-CDS)



11β, 17-dihydroxy-21-{[(1-methyl-1,4-dihydropyridin-3-yl)carbonyl]-oxy}pregn-4-ene-3,20-dione (hydrocortisone-CDS)

The aforenoted Bodor patents propose complexation with the specific cyclodextrin derivatives named in the preceding paragraph as a means for overcoming the stability problems from which the dihydropyridine-containing redox compounds suffer; the patents note that even in the dry state, the redox compounds are very sensitive to oxidation as well as to water addition. Such complexation is also proposed in the Bodor patents as a means for providing better brain to lung ratios of the redox compounds by preventing their precipitation out of solution at the injection site or in the lungs. Successful solubilization of a number of redox compounds is noted; however, Bodor indicates that such results are not universal. For example, in the case of estradiol, the redox derivative has about the same solubility in aqueous 50% hydroxypropyl-β-cyclodextrin as has the parent drug; in the case of norethindrone, the redox drug has less than 1% of the solubility in aqueous 50% hydroxypropyl-β-cyclodextrin displayed by the parent drug.

Bodor U.S. Patents Nos. 4,983,586, issued January 8, 1991, and 5,024,998, issued June 18, 1991, relate to pharmaceutical formulations for parenteral use. Aqueous parenteral solutions of drugs which are insoluble or only sparingly soluble in water and/or which are unstable in water, combined with cyclodextrin selected from the group consisting of hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of β- and γ-cyclodextrins, provide a means for alleviating problems associated with drug precipitation at the injection site and/or in the lungs or other organs following parenteral administration. The parenteral solutions contain from about 20% to about 50% of the selected cyclodextrin(s). The drugs may be the dihydropyridine forms of dihydropyridine $\rightleftharpoons$ pyridinium salt redox systems (as noted above in connection with the Bodor '935 and '566 patents) or other poorly soluble or unstable drugs of many types, including steroids. Anti-inflammatory steroids such as dexamethasone, hydrocortisone and prednisolone are mentioned.

Recently, the solubilizing and stabilizing effects of hydroxypropyl-β-cyclodextrin (HPβCD) on drugs have been reviewed by Thorsteinn Loftsson, Pharm. Ztg. Wiss. 4/136: 5-10 (1991). Solubility enhancement for many drugs in water has been accomplished by means of complexation with HPβCD. The solubility of dexamethasone was increased 5,500 times and intravenous administration of the dexamethasone-HPβCD complex gave higher initial plasma levels of dexamethasone than those obtained after dexamethasone phosphate dosing. The authors further note that transdermal/topical nonocclusive aqueous vehicle systems are suggested to avoid side-effects of occlusive systems, and that the improved water solubility of many lipophilic drugs in aqueous HPβCD solutions makes the nonocclusive systems possible. Transdermal delivery of the steroids 17β-estradiol, hydrocortisone and testosterone in aqueous HPβCD solutions have been reported. See also Loftsson et al, Acta Pharm. Nord. 1(4), 185-193 (1989), which describes the effects of 2-hydroxypropyl-β-cyclodextrin on the aqueous solubility of drugs, including dexamethasone, and the transdermal delivery of 17β-estradiol. It has also been suggested that the hydroxy-propyl derivatives of betacyclodextrin could be useful in solubilizing amino-substituted steroid therapeutic agents of the type disclosed in the aforementioned International Publication No. WO 87/01706 and U.S. Patent No. 5,124,154.

As previously noted, the literature has not suggested that hydroxyalkylated or branched cyclodextrin derivatives would be compatible with lightly crosslinked carboxy-containing polymers or that this combination of materials could be used to stabilize and solubilize pharmaceutical formulations of therapeutic agents to provide remarkably stable compositions whose drug release rate could be finely controlled.

SUMMARY OF THE INVENTION

The present invention provides a pharmaceutical composition comprising a therapeutic agent, an effective stabilizing amount of carboxy-containing polymer and cyclodextrin in an aqueous medium. The cyclodextrin is selected from the group consisting of the hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α, β and γ-cyclodextrin, modified or nonmodified.

It further provides a method for stabilizing and solubilizing a therapeutic agent in a pharmaceutical formulation, comprising combining the therapeutic agent in an aqueous medium with an effective stabilizing amount of carboxy-containing polymer and an amount of cyclodextrin sufficient to at least partially solubilize the therapeutic agent. The cyclodextrin is selected from the group consisting of the hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α, β- and γ-cyclodextrin, modified or nonmodified.

The present invention further provides a method for stabilizing and solubilizing an amino-substituted steroid therapeutic agent in a pharmaceutical formulation, comprising combining the therapeutic agent in an aqueous medium with an effective stabilizing amount of carboxy-containing polymer and an amount of cyclodextrin sufficient to at least partially solubilize the therapeutic agent. The cyclodextrin is selected from the group consisting of the hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α, β- and γ-cyclodextrin, modified or nonmodified.

In yet another aspect, the present invention provides a pharmaceutical composition comprising an amino-substituted steroid therapeutic agent selected from the group consisting of the C_{20} through C_{26} aminosteroids of the formula

XI hereinbelow, and the pharmaceutically acceptable salts, hydrates and solvates thereof, an effective stabilizing amount of a carboxy-containing polymer and an amount of cyclodextrin sufficient to at least partially solubilize said therapeutic agent, in an aqueous medium. The cyclodextrin being selected from the group consisting of the hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α, β- and γ-cyclodextrin, modified or nonmodified.

DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED EMBODIMENTS

This invention comprises pharmaceutical preparations containing a combination of carboxy-containing polymers and a molecular inclusion chemical entity, cyclodextrin or a derivative of cyclodextrin, particularly β-hydroxypropyl cyclodextrin, as a vehicle for delivering therapeutic agents. Drugs used in the formulation can be hydrophobic organic compounds with little solubility and they may be labile. The drug can also be a peptide or protein from either a recombinant process or synthetic process, or a water soluble drug. The advantages of the invention are most apparent, however, in connection with drugs having low solubility in water or body fluids and/or instability problems.

The combination of the present invention can be made without experiencing adverse consequences of incompatibility of the components. For instance, the improved solubility effect of the present invention might have been negated by the polymer competing for the drug. In addition to negating the desired improvement in solubility, and therefore bioavailability, undersirable precipitation or agglomerated of particles may have occurred.

The mechanism of the present invention is not fully understood and may be different for different therapeutic agents. It is believed, however, that

stabilization of the drug may be achieved by cyclodextrin through molecular inclusion of the drug in the cyclodextrin ring or by ionic attractive forces between the drug and cyclodextrin. The polymer component of the present invention, in most instances, provides the greatest stabilizing influence. For some drugs, particularly those that are positively charged, an ionic interaction may be formed between the drug and the polymer. This interaction may stabilize labile portions of the drug.

The drug can be partially or completely solubilized by β-hydroxypropyl cyclodextrin and/or other modified and nonmodified cyclodextrins. The term partial solubilization refers to a degree of solubilization in excess of the normal solubility for the particular drug. Increasing the solubility of therapeutic agents typically also reduces irritation that would otherwise be experienced. The degree of solubilization can be controlled by the type and weight fraction of the cyclodextrin and the manufacturing procedures used and the formulation. Although the present invention may incorporate drugs that are highly soluble in water and body fluids, the fullest advantage of the solubilizing effect of cyclodextrin will be realized in connection with drugs that have low solubility in water or body fluids.

Soluble drugs may be released from gels containing formulations of the present invention, through diffusion. Insoluble drugs can be solubilized by the cyclodextrin and diffused out of the polymeric gel or be released from it as the surrounding components of the formulation erode. By balancing the ratio between the solubilized and insoluble form of the drug in the formulation, the release profile of the drug from the delivery system can be modulated.

The amounts of cyclodextrin, carboxyl-containing polymer and drug may be varied to accommodate different applications. Other characteristics

such as pH and osmolality may also be tailored to suit requirements of particular applications. In general, however, a stabilized, solubilized drug delivery system will be an aqueous suspension at a pH of from about 3 to about 9, preferably about 5 to about 8. For ophthalmic applications an 6 osmotic pressure of from about 10 to about 400 mOsM is desirable. Generally, formulations may contain up to about 10%, more preferably about 0.1% to about 6.5% by weight, of the suspension, of a lightly cross-linked, carboxyl-containing polymer. Cyclodextrin may be present in amounts from about 1% to about 50%. Suspensions of the present invention may have a wide range of viscosities, but many formulations may have a viscosity of from about 1,000 to about 100,000 centipoises. For ophthalmic applications the viscosity will preferably be about 1,000 to about 30,000 centipoises for drops and about 30,000 to about 100,000 centipoises for ribbons. Viscosities greater than about 100,000 centipoises are ordinarily appropriate for topical routes of administration other than ophthalmic, e.g. dermal and local routes such as nasal, buccal, rectal and vaginal, but viscosities for these applications may also, in some instances, be lower than 100,000 centipoises.

In topical pharmaceutical formulations of the present invention, the polymer ranges from about 0.1 to about 10%, preferably about 0.1% to about 6.5% and more preferably about 0.5 to about 2%. The cyclodextrin preferably makes up about 1 to about 50%, more preferably about 5% to about 25%, depending on drug loading. Therapeutic agents (drugs) will ordinarily make up about .01% to about 10% by weight of the composition, preferably about 0.1% to about 5% of the composition.

The lightly cross-linked carboxy-containing polymers for use in the present invention are lightly cross-linked polymers of acrylic acid or the like and are, in general, well-known in the art. See, for example, Robinson U.S. Patent No. 4,615,697, and International Publication No. WO 89/06964,

referred to hereinabove. These polymers are also described in United States Patent 5,192,535.

Suitable polymers are ones prepared from at least about 90% and preferably from about 95% to about 99.9% by weight, based on the total weight of monomers present, of one or more carboxyl-containing monoethylenically unsaturated monomers. Acrylic acid is the preferred carboxyl-containing monoethylenically unsaturated monomer, but other unsaturated, polymerizable carboxyl-containing monomers, such as methacrylic acid, ethacrylic acid, β-methylacrylic acid (crotonic acid), cis-α-methylcrotonic acid (angelic acid), trans-α-methylcrotonic acid (tiglic acid), α-butylcrotonic acid, α-phenylacrylic acid, α-benzylacrylic acid, α-cyclohexylacrylic acid, β-phenylacrylic acid (cinnamic acid), coumaric acid (o-hydroxycinnamic acid), umbellic acid (p-hydroxycoumaric acid), and the like can be used in addition to or instead of acrylic acid. The most preferred polymers are lightly cross-linked carboxy polymers. As will be understood from the present disclosure, however, soluble carboxy polymers that are not cross-linked may also be used. Examples of soluble polymers of the present invention that are not cross-linked include polyacrylic acid polymers and polymethacrylic acid polymers. Such polymers may be made by known methods.

Preferred polymers are lightly cross-linked by using a small percentage, i.e., less than about 5%, such as from about 0.01% to about 5%, and preferably from about 0.2% to about 3%, based on the total weight of monomers present, of a polyfunctional cross-linking agent. Included among such cross-linking agents are non-polyalkenyl polyether difunctional cross-linking monomers such as divinyl glycol; 3,4-dihydroxy-hexa-1,5-diene; 2,5-dimethyl-1,5-hexadiene; divinylbenzene; N,N-diallylacrylamide; N,N-diallylmethacrylamide and the like. Also included are polyalkenyl polyether

cross-linking agents containing two or more alkenyl ether groupings per molecule, preferably alkenyl ether groupings containing terminal $H_2C=C<$ groups, prepared by etherifying a polyhydric alcohol containing at least four carbon atoms and at least three hydroxyl groups with an alkenyl halide such as allyl bromide or the like, e.g., polyallyl sucrose, polyallyl pentaerythritol, or the like; see, e.g., Brown U.S. Patent No. 2,798,053. Diolefinic non-hydrophilic macromeric cross-linking agents having molecular weights of from about 400 to about 8,000, such as insoluble di- and polyacrylates and methacrylates of diols and polyols, diisocyanate-hydroxyalkyl acrylate or methacrylate reaction products, and reaction products of isocyanate terminated prepolymers derived from polyester diols, polyether diols or polysiloxane diols with hydroxyalkylmethacrylates, and the like, can also be used as the cross-linking agents; see, e.g., Mueller et al U.S. Patents Nos. 4,192,827 and 4,136,250.

The lightly cross-linked polymers can of course be made from a carboxyl-containing monomer or monomers as the sole monoethylenically unsaturated monomer present, together with a cross-linking agent or agents. They can also be polymers in which up to about 40%, and preferably from about 0% to about 20% by weight, of the carboxyl-containing monoethylenically unsaturated monomer or monomers has been replaced by one or more non-carboxyl-containing monoethylenically unsaturated monomers containing only physiologically (and, where appropriate, ophthalmologically) innocuous substituents, including acrylic and methacrylic acid esters such as methyl methacrylate, ethyl acrylate, butyl acrylate, 2-ethylhexylacrylate, octyl methacrylate, 2-hydroxyethyl-methacrylate, 3-hydroxypropylacrylate, and the like, vinyl acetate, N-vinylpyrrolidone, and the like; see Mueller et al U.S. Patent No. 4,548,990 for a more extensive listing of such additional monoethylenically unsaturated monomers. Particularly preferred polymers are lightly cross-linked acrylic acid polymers wherein the cross-linking monomer

is 2,3-dihydroxyhexa-1,5-diene or 2,5-dimethylhexa-1,5-diene.

An especially preferred lightly cross-linked carboxy-containing polymer for use herein is polycarbophil, particularly NOVEON AA-1, a carboxyl-containing polymer prepared by suspension polymerizing acrylic acid and divinyl glycol. NOVEON AA-1 (also called Carbopol 976) is commercially available from The B.F. Goodrich Company. A different preferred lightly cross-linked carboxy-containing polymer for use herein is Carbopol 974P which is prepared using a different polyfunctional cross-linking agent (of the polyalkenyl polyether type).

The lightly cross-linked polymers used in practicing this invention are preferably prepared by suspension or emulsion polymerizing the monomers, using conventional free radical polymerization catalysts, to a dry particle size of not more than about 50 μm in equivalent spherical diameter; e.g., to provide dry polymer particles ranging in size from about 1 to about 30 μm, and preferably from about 3 to about 20 μm, in equivalent spherical diameter. In general, such polymers will range in molecular weight estimated to be greater than about 250,000 and preferably greater than about 2,000,000.

The cyclodextrins contemplated for use herein are hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of β-cyclodextrin and the corresponding derivatives of γ-cyclodextrin. The hydroxyalkyl groupings may contain one or more hydroxyl groups, e.g. hydroxypropyl (2-hydroxypropyl, 3-hydroxypropyl), dihydroxypropyl and the like. The glucosyl, maltosyl and maltotriosyl derivatives may contain one or more sugar residues, e.g. glucosyl or diglucosyl, maltosyl or dimaltosyl. Various mixtures of the cyclodextrin derivatives may be used as well, e.g. a mixture of maltosyl and dimaltosyl derivatives. Specific cyclodextrin derivatives for use herein include hydroxypropyl-β-cyclodextrin (HPCD or HPBCD),

hydroxyethyl-β-cyclodextrin (HEBCD), hydroxypropyl-γ-cyclodextrin (HPGCD), hydroxyethyl-γ-cyclodextrin (HEGCD), dihydroxypropyl-β-cyclodextrin (2HPBCD), glucosyl-β-cyclodextrin (G_1-β-CD or G_1BCD), diglucosyl-β-cyclodextrin ($2G_1$-β-CD or $2G_1$BCD), maltosyl-β-cyclodextrin (G_2-β-CD or G_2BCD), maltosyl-γ-cyclodextrin (G_2-γ-CD or G_2GCD), maltotriosyl-β-cyclodextrin (G_3-β-CD or G_3BCD), maltotriosyl-γ-cyclodextrin (G_3-γ-CD or G_3GCD) and dimaltosyl-β-cyclodextrin ($2G_2$-β-CD or $2G_2$BCD), and mixtures thereof such as maltosyl-β-cyclodextrin/dimaltosyl-β-cyclodextrin.

Hydroxypropyl-β-cyclodextrin for use in the compositions and methods of the present invention is commercially available. Alternatively, it can be prepared by known methods, especially by use of the optimized procedure of Pitha et al, International Journal of Pharmaceutics, 29, 73-82 (1986) or by modifications thereof as described in Bodor U.S. Patent No. 5,017,566 and related Bodor patents referred to hereinabove. The other hydroxyalkyl cyclodextrins intended for use herein can also be prepared by known procedures, e.g. as described by Pitha et al or Bodor. The cyclodextrins obtained in this manner are intrinsically amorphous mixtures; see Pitha et al, J. Pharm. Sci., Vol. 74, No. 9, September 1985, 987-990 and Pitha U.S. Patent No. 4,727,064.

The other cyclodextrins intended for use in the present invention, i.e. the glucosyl, maltosyl and maltotriosyl derivatives of α, β- and γ-cyclodextrin, modified or nonmodified, are branched cyclodextrins which are highly soluble in water as compared to the parent cyclodextrins. These branched cyclodextrins can be produced by microbiological processes from the parent cyclodextrins. Glucosyl-β-cyclodextrins can be obtained from the mother liquor of a large-scale β-cyclodextrin synthesis with Bacillus ohbensis cyclomaltodextrin glucanotransferase; see Koizumi et al, Chem. Pharm. Bull.,

35 (8), 3413-3418 (1987) and reference cited therein. Maltosyl and maltotriosyl β- and γ-cyclodextrins can be prepared from the parent cyclodextrin and maltose or maltotriose through the reverse action of Pseudomonas isoamylase or Klebsiella aerogenes pullulanase, while glucosyl-γ-cyclodextrin can be prepared by enzymatic hydrolysis of maltosyl-γ-cyclodextrin; see Okada et al, Chem. Pharm. Bull., 36 (6), 2176-2185 (1988) and references cited therein. The preparation of maltosyl-β-cyclodextrin by reacting maltose with β-cyclodextrin in the presence of pullulanase is also described in Japanese Kokai 61-287902, published Dec. 13, 1986, and Japanese Kokai 61-197602, published Sept. 1, 1986. A mixture of maltosyl-β-cyclodextrin and various dimaltosyl-β-cyclodextrins may be conveniently employed. See also Kainuma et al U.S. Patent No. 4,668,626, issued May 26, 1987.

A variety of drugs may be used in formulations of the present invention. Useful therapeutic agents include, but are not limited to: demulcents (for relief of "dry eye"), antibiotics, antivirals, steroids, amino-substituted steroids, including anti-inflammatory agents, peptides, polypeptides, cardiotonics, antihypertensives, or antioxidants, antiallergics, alpha- and betaadrenergic blocking agents, ophthalmic medicaments such as anticataract agents, collagenase inhibitors, antiglaucoma agents and ophthalmic antiinflammatory agents, ophthalmic lubricating agents, ophthalmic topical or regional anesthetic agents, antiretinopathy agents, etc.

More specific therapeutic agents believed suitable for use in the present invention include drugs such as idoxuridine, carbachol, bethanechol, timolol, atenolol, labetolol, metoprolol, nadolol, oxprenolol, pindolol, sotalol, betaxolol, acebutolol, alprenolol, levobunolol, p-aminoclonidine, dipivefrin, epinephrine, phenylephrine, phospholine, aceclidine, demecarium, cyclopentolate, homatropine, scopolamine, pilocarpine, ethacrynic acid,

furosemide, amiloride, bacitracin, neomycin, polymyxin, polymyxin B, gramicidin, gentamycin, penicillins, erythromycin, sulfacetamide, tobramycin, trospectomycin, vancomycin, ciprofloxacin, perfloxacin, olfloxacin, enoxacin, naphazoline hydrochloride, clindamycin, isofluorophate, fluorometholone, dexamethasone, hydrocortisone, fluorocinolone, medrysone, methylprednisolone, fluticasone propionate, betamethasone, estradiol, ibuprofen, flurbiprofen, naproxen, esters of ibuprofen, flurbiprofen, naproxen, ketorolac, suprofen, interferons, cromolyn, gancyclovir, aminozolamide, all trans-retinoic acid (Vitamin A) and the nontoxic, pharmaceutically acceptable salts thereof. Pro-drug counterparts are also within the scope of the present invention.

Topical or regional anesthetic agents include ones used during ophthalmic surgery or other ophthalmic procedures, such as lidocaine, cocaine, benoxinate, dibucaine, proparacaine, tetracaine, etidocaine, procaine, hexylcaine, bupivacaine, mepivacaine, prilocaine, chloroprocaine, benzocaine, tetracaine, and the like, as well as their acid forms.

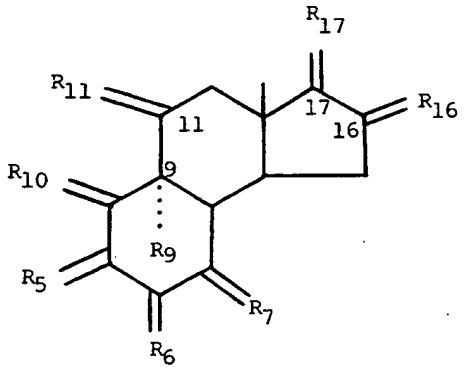
The drugs that may be administered include inorganic and organic drugs that can be transported across a vessel, for example, drugs acting on the central nervous system such as hypnotics and sedatives, mixtures thereof such as pentobarbital sodium, phenobarbital, secobarbital, thiopental, etc.; heterocyclic hypnotics such as dioxopiperidines, and glutarimides; hypnotics and sedatives such as amides and ureas exemplified by diethylisovaleramide and a bromo-isovaleryl urea; and hypnotic and sedative urethanes and disulfanes; narcotic antagonists such as naloxone and cyclazocine; psychic energizers such as isocarboxazid, nialamide, phenelzine, imipramine, tranylcypromine and paragylene; tranquilizers such as chloropromazine, promazine, fluphenazine, reserpine, deserpidine; meprobamate and benzodiazepines such as chlordiazepoxide; anticonvulsants such as primidone,

diphenylhydantoin, ethyltoin, phenetruide and ethosuximide; muscle relaxants and anti-parkinson agents such as mephenesin, methocarbomal, trihexylphenidyl, biperiden and levo-dopa, also known as L-dopa and L-β-3-4dihydroxyphenylalanine; analgesics such as morphine, codeine, meperidine and nalorphine, antipyretics and anti-inflammatory agents such as aspirin, salicylamide and sodium salicylamide; local anesthetics such as procaine, lidocaine, naepaine, piperocaine, tetracaine, and dibucane; antispasmodics and antiulcer agents such as atropine, scopolamine, methscopolamine, oxyphenonium, papaverine and prostaglandins such as PGE_1, PGE_2, PGF_{1a}, PGF_{2a}, and PGA; anti-microbials such as penicillin, tetracycline, oxytetracycline, chlortetracycline, and chloramphenicol; sulfonamides; anti-malarials such as 4-aminoquinolines, 8-aminoquinolines and pyrimethamine; antivirals including idoxuridine, hormonal agents such as prednisolone, prednisolone acetate, cortisone, cortisol and triamcinolone; androgenic steroids, for example methyltestosterone and fluoxmesterone; estrogenic steroids, for example, 17 β-estradiol and ethinyl estradiol; progestational steroids, for example, 17 α-hydroxyprogesterone acetate, 19-nor-progesterone, norethindrone and progesterone; sympathomimetic drugs such as epinephrine, amphetamine, ephedrine, and norepinephrine; cardiovascular drugs, for example, procainamide, amyl nitrite, nitroglycerin, dipyridamole, sodium nitrate, and mannitol nitrate; diuretics, for example, chlorothiazide, and flumethiazide; antiparasitic agents such as bephenium hydroxynaphthoate, dichlorophen, dapsone and enitabes; neoplastic agents such as mechlorethamine, uracil mustard, 5-fluorouracil, 6-thioguanine, and procarbazine; hypoglycemic drugs such as insulin, isophane insulin suspension, protamine zinc insulin suspension, globin zinc insulin, extended insulin zinc suspension, and other like insulins derived from animal and synthetic origin including tolbutamide, acetohexamide, tolazamide, and chlorpropamide; nutritional agents, for example vitamins such as ascorbic acid, essential amino acids, essential elements such as iron, and essential fats;

ophthalmic drugs such as pilicarpine base, pilocarpine hydrochloride, pilocarpine nitrate, eserine, eserine salicylate, atropine sulfate, homatropine, and eucatropine, and proteins or peptides such as human epidermal growth factor (hEGF), aFGF, bFGF, IL-1ra, TGF-β and gamma-interferon. The above drugs are further described in "The Pharmacological Basis of Therapeutics," edited by Goodman and Gilman, published by The Macmillan Company.

Compounds believed to be of particular interest in the present invention include [4(N-hydroxyamino)-2R-isobutyl-3S-(thienyl-thiomethyl) -succinyl]-L-phenylalanine-N-methylamide, ((5)-4-methyl-2-[methyl-[4-(2-methyl-imidazo[4,5-C]pyridin-1-ylmethyl)-benzene sulphonyl]-acetate, dexamethasone, erythromycin and hydrocortisone.

In the present invention, the amino-substituted steroid therapeutic agents employed are the C_{20} through C_{26} aminosteroids of formula XI (especially those which exhibit antioxidant functions), as set forth in International Publication No. WO87/01706 and in applicants' U.S. Patent No. 5,124,154, all of which are incorporated by reference herein in their entireties and relied upon. The intended aminosteroids have the formula



(XI)

where:

(A-I) R_6 is α-R_{61}:β-R_{62}, R_{10} is α-R_{101}:β-R_{102} and R_7 is α-H:β-H, where one of R_{61} and R_{62} is -H, and the other is -H, -F, or C_1-C_3 alkyl, R_{102} is $-CH_3$, R_{101} and R_5 taken together are $-(CH_2)_2-C(-R_{33})-CH=$ or $-CH-CH-CO-CH=$, where R_{33} is =O or α-H:β-OR_{34} or α-OR_{34}:β-H, where R_{34} is -H, $-P(=O)(OH)_2$, $-CO-CH_3$, $-CO-C_2H_5$, $-CO-C_6H_5$, $-CO-O-CH_3$ or $-CO-O-C_2H_5$;

(A-II) R_5 is α-R_{53}:β-R_{54}, R_6 is α-R_{63}:β-R_{64}, R_{10} is α-R_{103}:β-R_{104} and R_7 is α-H:β-H, where one of R_{63} and R_{64} is -H, and the other taken together with one of R_{53} and R_{54} forms a second bond between C_5 and C_6, R_{104} is $-CH_3$, R_{103} and the other of R_{53} and R_{54} taken together are $-(CH_2)_2-C(H)(OH)-CH_2-$ or $-(CH_2)_2-C[H][OP(=O)-(OH)_2]-CH_2-$;

(A-III) R_{10} and R_5 taken together are $=CH-CH=C(OR_3)-CH=$ where R_3 is -H, $-P(=O)(OH)_2$, C_1-C_3 alkyl, -CO-H, C_2-C_4 alkanoyl or benzyl, R_6 is α-R_{65}:β-R_{66} where one of R_{65} and R_{66} is -H, and the other is -H, -F, or C_1-C_3 alkyl and R_7 is α-H:β-H;

(A-IV) R_5 is α-R_{57}:β-R_{58}, R_6 is α-R_{67}:β-R_{68}, R_7 is α-H:β-H and R_{10} is α-R_{107}:β-R_{108}, where one of R_{57} and R_{58} is -H, R_{107} and the other of R_{57} and R_{58} taken together are $-(CH_2)_2-C(=R_{33})-CH_2$, where R_{33} is as defined above, R_{108} is $-CH_3$, where one of R_{67} and R_{68} is -H and the other is -H, -F, or C_1-C_3 alkyl;

(A-V) R_6 is R_{69}:R_{610}, R_7 is R_{79}:R_{710}, R_{10} is α-R_{109}:R_{1010}, where one of R_{69} and R_{610} is -H and the other taken together with one of R_{79} and R_{710} forms a second bond between C_6 and C_7, and the other of R_{79} and R_{710} is -H, R_{1010} is $-CH_3$, R_{109} and R_5 taken together are $-(CH_2)_2-C(=R_{33})-CH=$ or $-CH=CH-CO-CH=$, where R_{33} is as defined above; where:

(C-I) R_{11} is α-R_{111}:β-R_{112}, where one of R_{111} and R_{112} is taken together with R_9 to form a second bond between C_9 and C_{11} and the other of R_{111} and R_{112} is -H;

(C-II) R_9 is -Cl and R_{11} is =O or α-H:β-R_{114} where R_{114} is -Cl

or -OH;

(C-III) R_9 is -H or -F and R_{11} is =O or α-R_{115}:β-R_{116}, where one of R_{115} and R_{116} is -H, and the other of R_{115} and R_{116} is -H, -OH or C_1-C_{12} alkoxy;

(C-IV) R_9 is -H or -F and R_{11} is α-O-CO-R_{117}:β-H, where R_{117} is

(A) C_1-C_3 alkyl,

(B) C_1-C_{12} alkoxy,

(C) furanyl,

(D) -$NR_{122}R_{123}$, where one of R_{122} and R_{123} is -H, methyl or ethyl and the other is -H, C_1-C_4 alkyl or phenyl,

(E) -X_3-X_1, where X_3 is -O- or a valence bond, where X_1 is phenyl optionally substituted with 1 through 2 -Cl, -Br, C_1-C_3 alkoxy, -COOH, -NH_2, C_1-C_3 alkylamino, di(C_1-C_3)alkylamino, where the alkyl groups are the same or different, 1-pyrrolidinyl-, 1-piperidinyl, 1-hexamethylenimino-, 1-heptamethylenimino-, C_2-C_4 acylamino and -NH-CHO or with 1 -F or -CF_3;

where:

(D-I) R_{16} is R_{161}:R_{162} and R_{17} is R_{171}:R_{172}, where one of R_{161} and R_{162} is -H or -CH_3 and the other taken together with one of R_{171} and R_{172} forms a second bond between C_{16} and C_{17}, and the other of R_{171} and R_{172} is -C(=Z)-$(CH_2)_n$-$NR_{21}R_{210}$, where Z is =O, =CH_2 or R_{179}:-H where R_{179} is -H or -CH_3, where n is 0 through 6, where

(A) R_{21} is

(1) -$(CH_2)_m$-NR_{211}-X_2, where m is 2, 3 or 4, where R_{211} is -H or C_1-C_3 alkyl, where X_2 is: [A]

(a) pyridin-2-, 3- or 4-yl or the N-oxide thereof optionally substituted by 1 or 2 R_{212}, being the same or different, where R_{212} is

(i) -F,

(ii) -Cl,

(iii) -Br,

(iv) C_1-C_5 alkyl,

(v) $-CH_2-CH=CH_2$,

(vi) $-X_1$, where X_1 is as defined above,

(vii) $-NR_{213}R_{213}$ where the R_{213}'s are the same or different and are -H, C_1-C_3 alkyl or $-CH_2-CH=CH_2$,

(viiiα) $^*CH_2-(CH_2)_q-CH_2-N^*-$ where the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring, where q is 1 through 5,

(viiiβ) $^*CH_2-CH_2-(CH_2)_c-G-(CH_2)_d-CH_2-CH_2-N^*-$ where the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring, where G is -O-, -S-, -SO-, $-SO_2-$ or $-NHR_{214}$, where R_{214} is -H, C_1-C_3 alkyl, or X_1 as defined above, where c and d are the same or different and are 0 through 2 with the proviso that the total number of ring carbon atoms is 4, 5 or 6, [a]

(ix) 3-pyrrolin-1-yl, [b]

(x) pyrrol-1-yl optionally substituted with C_1-C_3 alkyl, [c]

(xi) piperidin-1-yl optionally substituted with 1 or 2 C_1-C_3 alkyl, [d]

(xii) 1,2,3,6-tetrahydro-pyridin-1-yl, [e]

(xiii) 1-hexamethyleneimino containing a 3- or 4- double bond or 3- and 5-double bonds, [f]

(xiv) 1,4-dihydro-1-pyridinyl substituted in the 4 position by two C_1-C_3 alkyl being the same or

different, [g]

(xv) -OH,

(xvi) C_1-C_3 alkoxy,

(xvii) $-NR_{217}-(CH_2)_e-Q$ where Q is 2-pyridinyl where R_{217} is -H or C_1-C_3 alkyl and e is 0 through 3 (1)

(xviii) pyridin-2-, 3- or 4-yl,

(b) 1,3,5-triazin-4-yl or the N-oxide thereof optionally substituted at the 2- and/or 6- position with R_{212} as is defined above, (4)

(c) pyrimidin-4-yl or the N-oxide thereof optionally substituted at the 2- and/or 6- position with R_{212} as is defined above, (5)

(d) pyrimidin-2-yl optionally substituted at the 4- and/or 6- position with 1 or 2 R_{212} as is defined above, (6)

(e) pyrazin-2-yl optionally substituted with 1 or 2 R_{212} as is defined above, (7)

(f) imidazol-2-yl optionally substituted in the 1 position with C_1-C_3 alkyl or $-X_1$, where X_1 is as defined above, and further optionally substituted with 1 or 2 R_{212} as defined above, (8)

(g) 1,3,4-triazol-2-yl optionally substituted in the 1 position with C_1-C_3 alkyl or $-X_1$, where X_1 is as defined above, and further optionally substituted with R_{212} as defined above, (9)

(h) imidazol-4- or 5-yl optionally substituted in the 1 position with C_1-C_3 alkyl or $-X_1$, where X_1 is as defined above, and further optionally substituted with 1 or 2 R_{212} as defined above, (10)

(i) benzo[b]thien-2-yl, (12a)

(j) indol-2-yl, (12b)

(k) benzo[b]thiazol-2-yl, (12c)

(l) benzimidazol-2-yl, (12d)

(m) 4-[2-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]ethyl]piperazinyl, (13)

(n) 1,2,4-triazin-3-yl optionally substituted at the 5- and/or 6- position with R_{212} as is defined above, (14)

(2) (1-piperazinyl)-(C_2-C_4)alkyl optionally substituted in the 4- position with -X_1 or -X_2 as defined above, [B]

(3) -X_2, as defined above, [O]

(4) -$(CH_2)_m$-X_4 where m is as defined above and where X_4 is

(a) -O-CH_2CH_2-Y, where Y is C_1-C_3 alkylamino, di(C_1-C_3)alkylamino where the alkyl groups are the same or different, C_3-C_6 alkyleneimino, optionally substituted with 1 or 2 C_1-C_3 alkyl,

(b) -$NR_{220}CH_2CH_2$-Y, where R_{220} is -H or C_1-C_3 alkyl and Y is as defined above,

(c) -$(CH_2)_g$-$N(R_{220})$-X_2, where g is 2, 3 or 4, and where R_{220} and X_2 are as defined above, [H]

(5) -$(CH_2)_m$-$NR_{222}R_{223}$, where R_{222} is -H or C_1-C_3 alkyl and R_{223} is -X_1 or -X_2 as defined above, or R_{222} and R_{223} are taken together with the attached nitrogen atom to form a saturated mono-nitrogen C_3-C_6 heterocyclic ring and where m is as defined above, [I]

(6) -$(CHCH_3)_b$-$(CH_2)_f$-R_{224}, where b is 0 and f is 1 through 3 or b is one and f is 0 through 3, where R_{224} is phenyl substituted with 1 through 3 -OH, C_1-C_3 alkoxy, -$NR_{225}R_{226}$ where R_{225} and R_{226} are the same or different and are -H, C_1-C_3 alkyl or are taken together with the attached nitrogen atom to form a C_4-C_7 cyclic amino

ring, [J]

(7) $-(CH_2)_i-X_2$, where i is 1 through 4 and X_2 is as defined above, [K]

(8) (1-piperazinyl)acetyl substituted in the 4-position by X_2 where X_2 is as defined above, [L]

(9) (1-piperazinyl)carbonylmethyl substituted in the 4- position by $-X_2$ where X_2 is as defined above, and [M]

(B) R_{210} is

(1) -H,

(2) C_1-C_3 alkyl,

(3) C_5-C_7 cycloalkyl,

(4) $-(CH_2)_m-NR_{211}-X_2$, where m, R_{211} and X_2 are as defined above, [A]

(5) (1-piperazinyl)-(C_2-C_4)alkyl optionally substituted in the 4- position with $-X_1$ or $-X_2$ as defined above, [B]

(6) $-(CH_2)_m-X_4$, where m and X_4 are as defined above, [H]

(7) $-(CH_2)_m-NR_{222}R_{223}$, where m, R_{222} and R_{223} are as defined above, [I]

(8) $-(CHCH_3)_b-(CH_2)_f-R_{224}$, where b, f and R_{224} are as defined above, [J]

(C) R_{21} and R_{210} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of

(1) 2-(carboxy)-1-pyrrolidinyl optionally as the C_1-C_3 alkyl ester or as a pharmaceutically acceptable salt, [C-1]

(2) 2-(carboxy)-1-piperidinyl optionally as the C_1-C_3 alkyl ester or as a pharmaceutically acceptable salt [C-2]

(3) 2-(carboxy)-1-hexamethyleneimino optionally

as the C_1-C_3 alkyl ester or as a pharmaceutically acceptable salt, [C-3]

(4) 2-(carboxy)-1-heptamethylene-imino optionally as the C_1-C_3 alkyl ester or as a pharmaceutically acceptable salt, [C-4]

(5) 1-piperazinyl substituted in the 4- position with R_{228}-CO-$(CH_2)_j$- where R_{228} is -X_1, -$NR_{229}X_1$ or 2-furanyl, where R_{229} is -H or C_1-C_3 alkyl, where j is 0 through 3 and X_1 is as defined above, [D]

(6) 1-piperazinyl substituted in the 4- position with X_2-$(CH_2)_j$-, where X_2 and j are as defined above, [E]

(7) 1-piperazinyl substituted in the 4- position with X_1-(CH_2)j-, where X_1 and j are as defined above, [F]

(8) 4-hydroxy-1-piperidinyl substituted in the 4- position with X_1 as defined above, [G]

(9) 1-piperazinyl substituted in the 4- position with X_2-NR_{229}-CO-$(CH_2)_i$-, where X_2, R_{229} and i are as defined above; [N]

(D-II) R_{16} is α-R_{163}:β-R_{164} where one of R_{163} and R_{164} is -H and the other is -H, -F, -CH_3 or -OH, and R_{17} is -CH-$(CH_2)_p$-$NR_{21}R_{210}$, where p is 1 or 2, where R_{21} and R_{210} are as defined above;

(D-III) R_{16} is α-R_{165}:β-R_{166} and R_{17} is α-R_{175}:β-R_{176}, where R_{165} is -H, -OH, -F or -CH_3 and R_{166} is -H, -OH, -F, or -CH_3, with the proviso that at least one of R_{165} and R_{166} is -H, where R_{175} is -H, -OH, -CH_3, -CH_2CH_3, C_2-C_7 alkanoyloxy or -O-CO-X_1, where X_1 is as defined above, and where R_{176} is -C(=Z)-(CH_2)n-$NR_{21}R_{210}$, where Z, n, R_{21} and R_{210} are as defined above;

(D-IV) the 16,17-acetonide of a compound where R_{165} is -OH, R_{166} is -H, R_{175} is -OH and R_{176} is -C(=Z)-$(CH_2)_n$-$NR_{21}R_{210}$, where Z,

n, -R_{21} and R_{210} are as defined above;

and pharmaceutically acceptable salts thereof,

and hydrates and solvates thereof;

with the following overall provisos that:

(I) one of R_{161} or R_{162} is taken together with one of R_{171} or R_{172} to form a second bond between C_{16} and C_{17}, only when R_{10} is α-R_{101}:β-R_{102}, α-R_{103}:β-R_{104}, α-R_{107}:β-R_{108} or α-R_{109}:β-R_{1010},

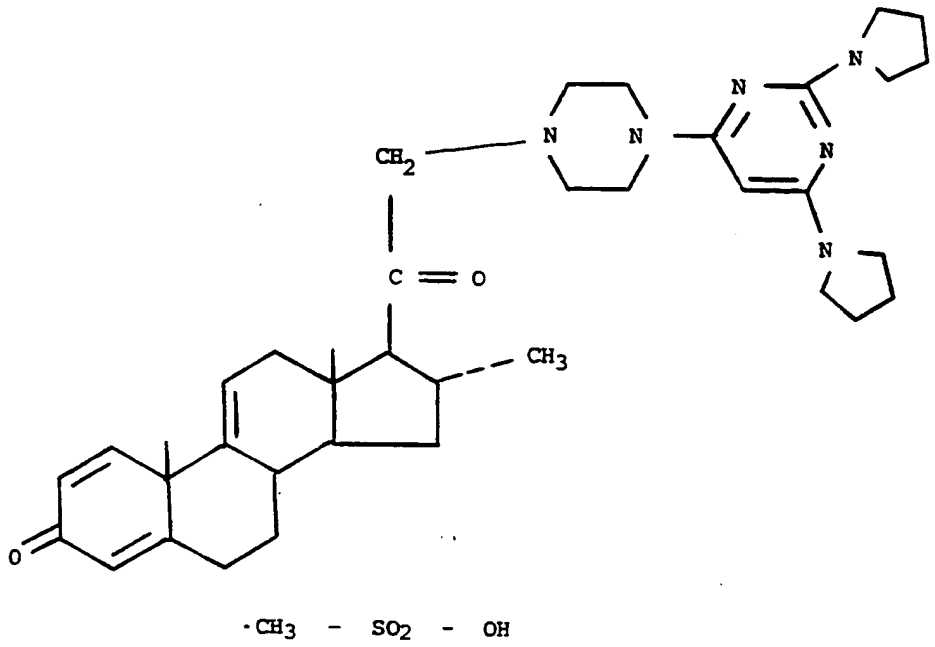
(II) R_{17} is -CH-$(CH_2)_p$-$NR_{21}R_{210}$, only when R_{10} is α-R_{101}:β-R_{102}, a-R_{103}:β-R_{104}, α-R_{107}:β-R_{108} or α-R_{109}:β-R_{1010},

(III) R_5 and R_{10} taken together are =CH-CH=C(OR_3)-CH=, only when R_{17} is α-R_{175}:β-R_{176} or the 16,17-acetonide of a compound where R_{16} is α-OH:β-H and R_{17} is α-OH:β-C(=Z)-$(CH_2)_n$-$NR_{21}R_{210}$, and

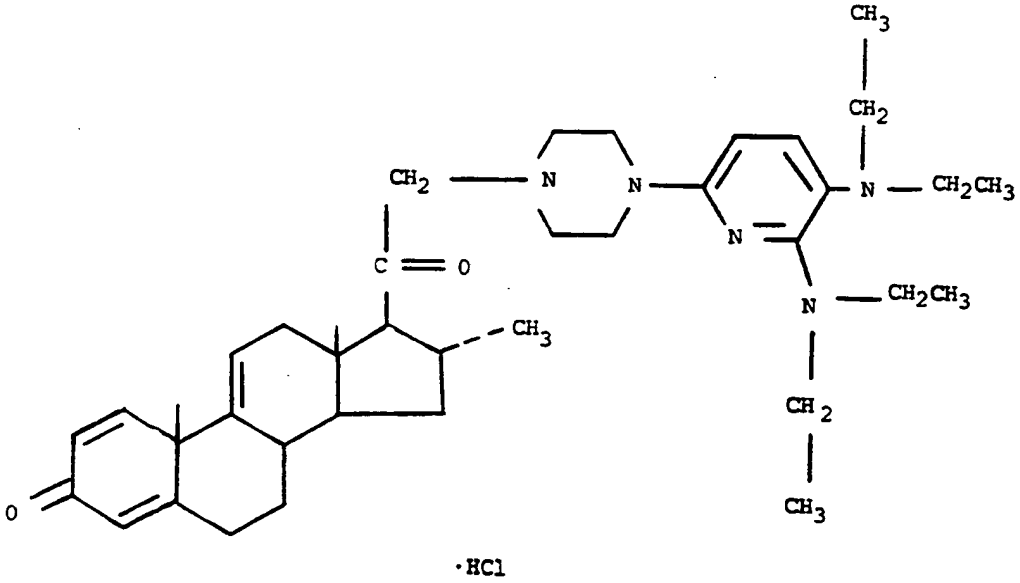
(IV) R_5 is α-R_{57}:β-R_{58}, only when R_{17} is α-R_{175}:β-R_{176} or α-OH:β-C-(=Z)-$(CH_2)_n$-$NR_{21}R_{210}$, or the 16,17-acetonide thereof.

More preferred are the C_{21} aminosteroids of formula XI, especially those which inhibit lipid peroxidation. Most preferred are the 21-[4-(substituted-4-pyrimidinyl)-1-piperazinyl]-steroids, such as U-74006 (21-[4-(2,6-dipyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione), and the 21-[4-(substituted-2-pyridinyl)-1-piperazinyl]-steroids, such as U-74500 (21-[4-[5,6-bis(diethylamino)-2-pyridinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione)and U-75412 (21-[4-(3-ethylamino-2-pyridinyl)-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione), all, when in the unformulated state, preferably as a solid, preferably crystalline, preferably relatively non-hygroscopic and pharmaceutically acceptable salts, such as the methanesulfonate salt of U74006 (U-74006F), the hydrochloride of U-74500 (U-74500A), and the hydrochloride or maleic acid salt of U-75412 (U-75412A and U-75412E, respectively); See Braughler et al, Biochemical Pharmacology 37: 3853-3860 (1988). The

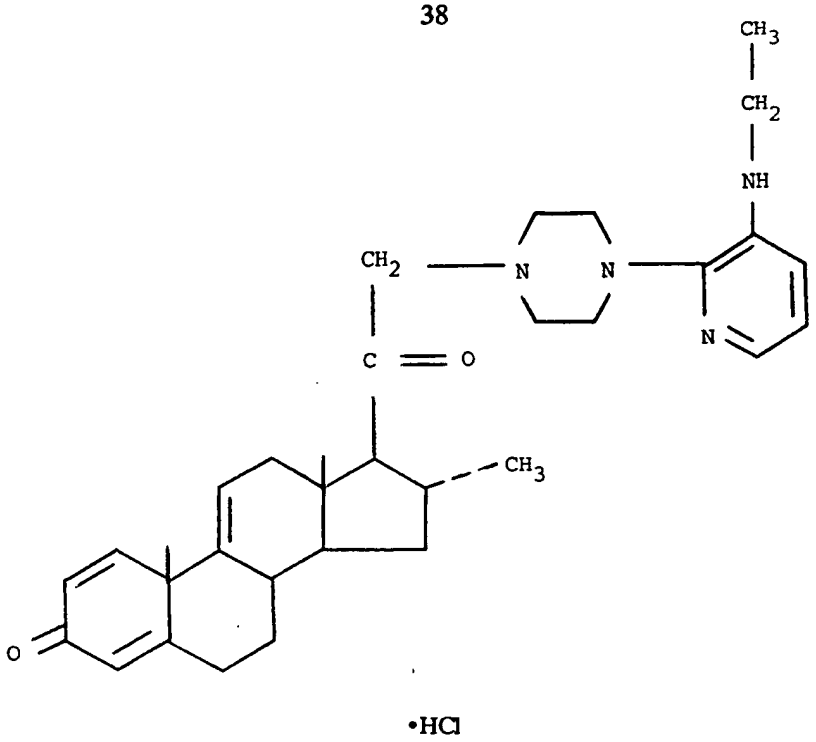
following are illustrative structures.



·CH3 - SO2 - OH

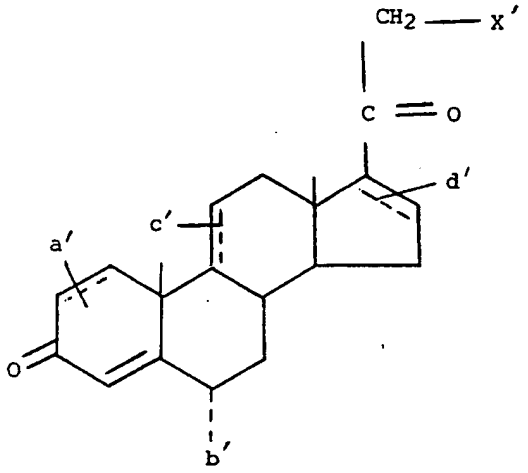


·HCl



•HCl

The above-preferred amino steroids are all exemplified as 21-substituted-16α-methylpregna-1,4,9(11)-triene-3,20-diones. However, the steroidal portion of these may be modified without substantially altering their preferred nature. Thus, a class of preferred C_{21} amino-substituted steroids may be represented by the formula I, below



(I)

where:

a′ is selected from the group 1,2-dihydro (saturated) and 1,2-dehydro (1,2-double bond);

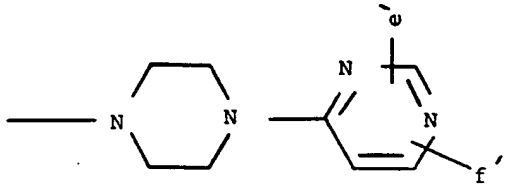
b′ is selected from the group 6α-H, 6α-methyl and 6α-flouro;

c′ is selected from the group 9,11-dihydro (saturated), 9(11)-dehydro (double bond), 9α-H-11α-OH-11β-H,9α-H-11β-OH-11α-H,9α-H-11-keto,9α-F-11β-OH-11α-H and 9α-F-11-keto;

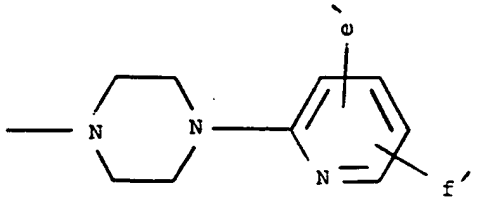
d′ is selected from the group 16α-methyl-16β-H-17α-H, 16β-methyl-16α-H-17α-H, 16-H_2-17α-H, 16-H-16,17-dehydro (double bond), and 16-methyl-16,17-dehydro. Less preferably, a 17α-OH group can be present instead of 17α-H when d′ is not 16-H-16,17-dehydro or 16-methyl-16,17-dehydro; and where:

X′ is selected from the complex 21-amino substituents X1′ and X2′ where

X1′ is



and

X2′ is 

where e′ and f′ may be the same or different and are selected from the group: H,NHR1′ and NR1′R2′, where R1′ and R2′ are C1 to C3 lower alkyl or R1′ and R2′, taken together with N, constitute a heterocyclic ring; preferably 1-ethyleneimino, 1-trimethyleneimino, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl and 1-(4-methyl)piperazinyl.

Pharmaceutically acceptable salts of the aminosteroids of formula (XI) are frequently preferred over the fee base form because the salts are more soluble in water and form crystals which are better suited to pharmaceutical use. Preferred salts are those prepared by reacting the free base of the aminosteroid of formula (XI) with an approximately stoichiometrical amount of a pharmaceutically acceptable acid such as hydrochloric, hydroiodic, hydrobromic, phosphoric, sulfuric, acetic, citric, lactic, succinic, benzoic, pamoic, salicylic, cyclohexanesulfamic, methanesulfonic, p-toluenesulfonic, naphthalenesulfonic, malic, oxalic, fumaric or the like. Preferred salts are those of hydrochloric, methanesulfonic, maleic and fumaric acids.

Equivalent to the steroids of formula (XI) and their pharmaceutically acceptable acid addition salts for the purposes of this invention are the pharmaceutically acceptable hydrates or solvates thereof, in which form they can be isolated.

The aminosteroids can be administered by a variety of routes for the treatment or prevention of a variety of conditions, as noted in International Publication No. WO 87/01706. For particular routes of administration, certain characteristics of the lightly cross-linked polymers need to be carefully controlled. Thus, for example, aqueous suspensions containing polymer particles prepared by suspension or emulsion polymerization whose average dry particle size is appreciably larger than about 50 μm in equivalent spherical diameter are less comfortable when administered to the eye than suspensions otherwise identical in composition containing polymer particles whose equivalent spherical diameters are, on the average, below about 50 μm. It has also been discovered that lightly cross-linked polymers of acrylic acid or the like prepared to a dry particle size appreciably larger than about 50 μm in equivalent spherical diameter and then reduced in size, e.g., by mechanically milling or grinding, to a dry particle size of not more than about 50 μm in equivalent spherical diameter do not work as well as polymers made by suspension or emulsion polymerization.

In some preferred embodiments of the invention, the particles have a narrow particle size distribution within a 10μm band of major particle size distribution which contains at least 80%, more preferably at least 90%, most preferably at least 95% of the particles. Also, there is no more than 20%, preferably no more than 10%, and most preferably no more than 5% particles of a size below 1 μm. The presence of large amounts of such fines has been found to inhibit the desired gelation upon eye contact. Apart from that, the use of a monodispersion of particles will give maximum viscosity and an increased eye residence time of the ophthalmic medicament delivery systems for a given particle size. Monodisperse particles having a particle size of 30 μm and below are most preferred. Good particle packing is aided by a narrow particle size distribution.

Aqueous solutions and suspensions for liquid oral administration will typically contain between about 0.05 and 5.0% by weight, preferably between 0.1 and 2.0% by weight of the amino-substituted steroid therapeutic agent; that suitable adjuvants which may be used as carriers to provide wetability and stability include propylene glycol, lightly cross-linked carboxy-containing polymers such as polycarbophil, ethyl cellulose, hydroxypropyl cellulose and methyl cellulose; and that other additives, including sodium edetate, methyl and propyl parabens, flavoring agents and colorants may also be employed, if desired. Examples 7 and 8 in the parent and grandparent applications detail the preparation of topical compositions containing the aminosteroid U-74006F, U-74500A or U-75412A and a polycarbophil (NOVEON AA-1). A viscosity of 5,000 cps or greater is noted in Example 7. Sodium chloride, EDTA, sodium hydroxide and, optionally, the preservative benzalkonium chloride are also present in the compositions.

In accordance with the invention, a stabilized sustained release aminosteroid delivery system comprises an aqueous suspension at a pH of from about 3 to about 9 (preferably 5 to 8) and an osmotic pressure of from about 10 to about 400 mOsM containing from about 0.1% to about 6.5% by weight, based on the total weight of the suspension, of a lightly cross-linked, carboxyl-containing polymer prepared by polymerizing one or more carboxyl-containing monoethylenically unsaturated monomers and less than about 5% by weight of a cross-linking agent, such weight percentages of monomers being based on the total weight of monomers polymerized. Typically, the suspension has an initial viscosity of from about 1,000 to about 30,000 centipoises and is administrable to the eye in drop form, or in the form of a ribbon at a viscosity of from about 30,000 to about 100,000 centipoises, but considerably higher viscosities are acceptable for topical routes of administration other than ophthalmic, e.g. dermal, and local routes such as nasal, buccal, rectal and vaginal. The polymer has an average particle size

of not more than about 50 μm, preferably not more than about 30 μm, in equivalent spherical diameter. In the case of topical ophthalmic delivery systems, the pH of the suspension is from about 5 to about 9. The viscous gel can remain in the eye for a prolonged period of time so as to release the aminosteroid therapeutic agent contained therein in sustained fashion.

The polymer is preferably prepared from at least about 50% by weight, more preferably at least about 90% by weight, of one or more carboxyl-containing monoethylenically unsaturated monomers. Desirably, the polymer is prepared by suspension or emulsion polymerizing acrylic acid and a non-polyalkenyl polyether difunctional cross-linking agent to a particle size of not more than about 50 μm, preferably not more than about 30 μm, in equivalent spherical diameter. A preferred cross-linking agent is divinyl glycol. It may be desirable to replace up to about 40% by weight of the carboxyl-containing monoethylenically unsaturated monomers by one or more non-carboxyl-containing monoethylenically unsaturated monomers containing only physiologically (and, where appropriate, ophthamologically) innocuous substituents.

The osmotic pressure is preferably achieved by using a physiologically (and, where appropriate, ophthalmologically) acceptable salt in an amount of from about 0.01% to about 1% by weight, based on the total weight of the suspensions. A preferred salt is sodium chloride.

Aminosteroid of formula (XI) may be present in desired therapeutic amount, preferably from about 0.01% to about 10% by weight, based on the total weight of the suspension. Preferred aminosteroids include U-74006, U-74500, U-75412, U-74006F, U-74500A, U-75412A and U-75412-E and aminosteroids of forumula I.

In a preferred method of preparing stable sustained release topical ophthalmic delivery systems, the foregoing suspensions are prepared and packaged at the desired viscosity of from 1,000 to about 30,000 centipoises, for administration to the eye in drop form. Upon administration to the eye, viscous gel remains in the eye for a prolonged period of time so as to release in a sustained fashion the aminosteroid entrapped therein.

The present invention thus provides a stable ophthalmic delivery system that not only has the benefits of administration in drop form, but also does not suffer from breakdown limitations due to administration at a viscosity suitable for drops. Through administration at a viscosity such that the suspension can be reliably administered in drop form, but which actually increases when the suspension is so administered, controlled release of aminosteroid medicament is significantly enhanced.

As mentioned above, viscosities substantially over 30,000 cps are generally not suitable for drops; also, viscosities over 100,000 are generally not suitable as ribbons. When the viscosities are substantially lower than 1,000 cps, the ability of the gel to sustain itself after contact with tears is impeded. When a suspension at a pH of from about 3 to about 6.5 and an osmotic pressure of from about 10 to about 400 mOsM contacts the tear fluid, there is an increased gelation with a pH change. As will be appreciated, tear fluid is at a higher pH of about 7.2 to about 7.4. With the pH increase, carboxylic acid (COOH) undergoes a sodium replacement (to COONa), and the sodium form dissociates, causing the polymer to expand.

The relationships between the degree of cross-linking and between the degree of cross-linking and particle size can become quite important variables. Because the particles are present in a suspension, the degree of cross-linking is necessarily high enough to avoid substantial dissolution of the polymer. On

the other hand, since rapid gelation may be achieved at the time of a pH change, the degree of cross-linking is necessarily low enough to permit gelation. Moreover, if the polymer particle size is too large, induced swelling can tend to fill voids between large particles that are in contact with one another, rather than causing gelation.

If the polymer were in a dissolved state, as it would be if there were insufficient cross-linking because the ratio of cross-linker to monomer was too low, particle size would be basically irrelevant. In a suspension, particle size can be relevant to comfort. However, it has been found that in the system of the present invention, the small particle size and light cross-linking synergistically yield rapid gelation to a substantially increased viscosity when the pH changes such as when compositions of the present invention contact tears fluid. In fact, above the 50 μm size this advantage of substantially increased viscosity is not realized. Moreover, at the 50 μm size, there is also reasonably good eye comfort.

In a most preferred form of the invention, the particles are not only subject to the upper size limits described above, but also to a narrow particle size distribution. Such use of a monodispersion of particles, which aids in good particle packing, yields a maximum increased viscosity upon contact of the suspension with the tears and increases eye residence time. At least about 80%, more preferably at least about 90% and most preferably at least about 95%, of the particles should be within a no more than about 10 μm band of major particle size distribution, and overall (i.e., considering particles both within and outside such band) there should be no more than about 20%, preferably no more than about 10% and most preferably no more than about 5% fines (i.e., particles of a size below 1 μm). It is also preferred, as the average particle size is lowered from the upper limit of 50 μm, more preferably 30 μm, to lower sizes such as 6 μm, that the band of major particle

size distribution be also narrowed, for example to 5 μm. Preferred sizes for particles within the band of major particle distribution are less than about 30 μm, more preferably less than about 20 μm, most preferably from about 1 μm to about 5 μm.

It is apparent that, while the stable sustained delivery systems discussed above are uniquely well-suited to ophthalmic administration, the same systems can be used for topical treatment of skin and mucous membrane by local application to tissue in need of treatment, such as dermal, nasal, vaginal and rectal tissues. However, various features of the systems designed for administration to the eye can be modified in order to produce systems which are even better suited to the contemplated non-ophthalmic route of administration. For example, larger amounts of cross-linking agents and/or higher pH levels may be utilized to provide more viscous gels suited for longer retention on the skin or in body cavities. Furthermore, when it is desired to combine in a single composition the sustained release and prolonged retention properties of the aminosteroid suspensions described above with the immediate release which aminosteroid solutions would provide, or when it is desired to simply achieve the more immediate release and greater penetration possible with solutions, be it for ophthalmic or other route of administration, yet other modifications of the invention can be made as described in more detail hereinbelow.

As noted hereinabove, the stable compositions obtained in accord with the foregoing detailed description provide for sustained release of the aminosteroid, by virtue of the fact that the aminosteroid is in suspension; prolonged retention at the site of application can also be readily provided by these compositions by virtue of their viscosity. However, immediate release of the aminosteroid and greater penetration (e.g. through the cornea or skin, in the case of ophthalmic or dermal application, respectively) are sometimes

desired, either in combination with or instead of the sustained release/prolonged retention properties. The present invention provides for modification of the method and compositions described above in order to achieve these goals. Specifically, the aminosteroid can be partially or completely solubilized in the aminosteroid/lightly cross-linked carboxy-containing polymer formulations by using an amount of cyclodextrin (as defined and discussed in detail hereinabove) sufficient to at least partially solubilize the aminosteroid. Addition of cyclodextrin reduces irritation topically and ocularly. Moreover, if desired, sufficient cyclodextrin can be utilized to substantially completely solubilize the aminosteroid. The degree of solubilization can be controlled and the mixed solution/suspension or complete solution which results is stable to degradation. The cyclodextrin used can be any of the hydroxyalkylated or branched derivatives of β- and γ-cyclodextrins identified hereinabove. However, hydroxypropyl-β-cyclodextrin is presently preferred.

When compositions of the present invention are suspensions or formulations intended for administration to the eye, particle size and viscosity of the polymers, may be less important particularly when the therapeutic agent is completely solubilized. The cyclodextrin-containing compositions of the present invention can be adapted for topical treatment of skin and mucous membrane by local application to tissue in need of treatment, such as dermal, nasal, vaginal and rectal tissues. The dosage loading for compositions of the present invention may vary depending on the drug used, the route of administration selected and other factors familiar to those skilled at methods of formulating pharmaceutical compositions.

In a typical method for stabilizing and partially or completely solubilizing aminosteroids in accord with the present invention, the selected cyclodextrin (e.g. hydroxypropyl-β-cyclodextrin) is employed in an amount

sufficient to solubilize at least a portion of the aminosteroid in the final formulation; the cyclodextrin is thus utilized in an amount which is generally from about 1.0 to about 20.0% or 30.0% by weight of the total composition, but much larger amounts of cyclodextrin (e.g. up to about 50% by weight) may be used when complete solubilization is desired, depending on the insolubility of the particular aminosteroid selected, the amount of aminosteroid to be solubilized and the solubilizing power of the selected cyclodextrin. The weight ratio of cyclodextrin to aminosteroid can range from about 1:1 to about 500:1. The selected polymer is generally used in an effective stabilizing amount of from about 0.1% to about 2% by weight of the final composition, although additional polymer (up to about 6.5% by weight) can be present, if desired. This amount can also to expressed as a weight to weight ratio of polymer to aminosteroid from about 1:10 to about 20:1. Generally, the cyclodextrin is dissolved in water, then the polymer is slowly dispersed therein and stirred (typically, for a period of from about 15 minutes to 2 hours). Sodium chloride (from about 0 to 0.9% by weight) is added to adjust osmolality and, optionally, EDTA may be added to complex metal ions. The resultant mixture is generally heated (e.g. autoclaved) for a period of from about 30 to about 90 minutes, then cooled. It is preferred to adjust the pH of the mixture to be above about 6. This may be done by addition of a suitable base such as sodium hydroxide. Separately, the aminosteroid (from about 0.01 to about 10.0% by weight of the total composition) is dissolved in a strong acid solution (e.g. aqueous hydrochloric acid) and that solution is combined with the polymer/cyclodextrin solution, the pH is adjusted to around pH 6-7 with sodium hydroxide, and water is added as necessary to bring the total volume to 100%. Compositions obtained in this manner can be solutions or mixed suspensions/solutions; the degree of solubilization is controlled by the concentration of the cyclodextrin component. A representative formulation prepared as described in EXAMPLE 1 hereinbelow, having a 1% w/w concentration of the representative aminosteroid U-74006F which is

approximately 75% solubilized, will be stable at room temperature and at 40°C over a three month storage period. There is no significant loss of aminosteroid concentration at either temperature. In this case, it is believed that stability results from the stability of the non-dissolved aminosteroid, the interaction of the aminosteroid with the polymer as discussed above in relation to the non-cyclodextrin compositions, and the molecular inclusion of the aminosteroid by the cyclodextrin. Solubilization is of course due primarily to the presence of cyclodextrin. The main reason the aminosteroid is stable in both formulations appears to be the presence of the cross-linked polymer and its ionic interaction with the aminosteroid.

The aminosteroids of formula XI are useful in the treatment of a variety of medical conditions in warm-blooded animals, including humans. The present invention provides pharmaceutical compositions for administration in the treatment or prevention of the various conditions for which the aminosteroids are known to be useful, e.g. from International Publication No. WO 87/01706, and from U.S. Patent No. 5,124,154. Briefly, such conditions include spinal trauma; head injury (mild, moderate or severe); subarachnoid hemorrhage (including the associated cerebral vasospasm); skin graft rejection; ischemic stroke; excessive mucous secretion; asthma; muscular dystrophy; shock (hemorrhagic, septic or traumatic); cardiac toxicity induced by anti-cancer agents such as adriamycin; Parkinsonism, Alzheimer's disease and other neurological disorders of a degenerative nature; severe burns; ARDS; multiple sclerosis; organ damage occurring during reperfusion following transplant; osteoarthritis, rheumatoid arthritis and other inflammatory diseases; dermatological disorders such as inflammation and psoriasis; immunological nephrotic syndrome; allergic reactions; systemic lupus erythematosis; atherosclerosis; emphysema; metastases and tumor growth; cluster headaches, ulcers induced by stress; complications from radiation damage, brain tumors and damage after myocardial infarction; and burns and wounds (to promote

healing). The aminosteroids are further known to be useful in the prevention of damage following cardiopulmonary resuscitation, cardiac infarction and neurological or cardiovascular surgery; in the treatment and prevention of many of the conditions for which glucocorticoid pharmaceuticals are known to be useful (some of which are listed hereinabove); in the treatment or prevention of ophthalmic diseases or disorders such as cataracts, glaucoma or the risk of glaucoma associated with significantly elevated intraocular pressure, inflammatory eye disease, retinal eye disease, intraocular pressure rise due to uveitis, post-infarct ambolus, traumatic eye injury (such as blunt trauma, compression injury, hyphema, surgical trauma, etc.), neovascular or ischemic eye disease (conditions in the eye involving ischemia such as corneal edema from prolonged wearing of contact lenses and the like), bullous keratitis, dry eye including keratitis sicca, alkali burn and conditions arising from transplantation of ocular cells.

The foregoing is not meant to imply that each of the aminosteroids of formula XI is useful for every condition noted above. However, one skilled in the art can readily ascertain which aminosteroids are useful for which purposes, for example, using assay procedures referred to in International Publication No. WO 87/01706.

Routes of administration, frequency of administration and dosage levels vary with the particular therapeutic agent selected, condition being treated, severity of the condition, size, weight and age of the patient and other well-known factors. Typical dosage ranges for intravenous or intramuscular injection of aminosteroids include from about 0.05 to about 100 mg/kg/day, one to four times daily. The dosages will vary, of course, with the compound selected. Obviously, suspension and solutions can be administered by other routes as well including topical (e.g., ophthalmic, dermal or vaginal), introcular, nasal and rectal administration.

Topical administration to the skin is generally preferred for the treatment of many dermatological conditions, particularly skin inflammation and psoriasis, but particularly serious dermal conditions may require systemic administration, alone or in conjunction with topical treatment. Here again, the specific dosages selected will vary somewhat depending on the drug selected and other factors noted above.

In the case of ophthalmic conditions, topical administration is preferable when the target of the treatment is located in or near the anterior chamber of the eye. By contrast, because the flow of aqueous humor is from the ciliary body (behind the iris) forward towards the cornea before it exits through the trabecular meshwork and Schlemm's canal, penetration of drugs to the back of the eye when administered topically to the front of the eye occurs with some difficulty. It is therefore often more effective to administer drugs intended for the treatment of uveal and retinal diseases by the systemic route where access to the eye occurs through the choroid plexus, or by the intravitreal route. Some of the more severe eye diseases affect those targets which are difficult to treat effectively by the topical route and they can be associated with markedly impaired vision or blindness. Accordingly, the topical route is preferred for convenience of individual patient self-administration, and the intraocular and systemic routes are preferred for surgical and presurgical administration.

In order to maintain an ocularly adequate therapeutic level of drug in the back of the eye where surgery is not involved, or has been concluded, the present invention also contemplates the treatment of an ophthalmic disease by administration of a therapeutically effective amount of amino-substituted steroid antioxidant agent (including salts, hydrates or solvates), by oral or intramuscular routes, in addition to the convenient topical route or by intraocular injection.

Aqueous solutions, aqueous suspensions, ointments, and gels are preferably used for topical formulations, e.g. for ophthalmic or dermal administration. The aqueous formulations may also contain liposomes for creating a reservoir of dissolved amino-substituted steroid therapeutic agent for contact with the tear film. Particularly preferred among topical formulations are gels, which enhance pre-corneal retention and protect the amino-substituted steroids from degradation without the inconvenience and impairment of vision associated with ointments.

Topical formulations should generally include between 0.01 and 10% by weight, preferably between 0.1 and 5% by weight, of the amino-substituted steroid therapeutic agent, together with the amounts of polymer and/or cyclodextrin noted hereinabove, in an aqueous medium.

Other additives which are desirably included in the topical formulations include sodium chloride, EDTA (disodium edetate), pH adjusters, buffers, surfactants, and preservatives like BAK (benzalkonium chloride). Administration of the formulation to the eye or skin will typically be carried out between one and four times a day, depending on the particular problem being treated.

Formulations for ocular injection, intramuscular injection, oral administration and other routes can be formulated in accord with techniques well-known to those skilled in the art of pharmaceutical formulations. The amounts of therapeutic agent, polymer and cyclodextrin as noted hereinabove may typically be included in an aqueous medium; and as in the case of topical formulations, other additives may be included just so long as they do not interfere with the stabilization (and solubilization, when desired) and are appropriate for the selected route of administration. See, for example applicants' parent application referenced hereinabove, and Remington's

Pharmaceutical Sciences, seventeen edition, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, PA (1985) which is incorporated herein by reference in its entirety and is relied upon.

The following examples are given for illustrative purposes only and should in no way be construed as limiting the subject matter presently disclosed and claimed.

EXAMPLE 1

A 100 g batch of pharmaceutical composition may be prepared as described below:

INGREDIENT	CONCENTRATION (% w/w)
Aminosteroid U-74006F	1.0%
Polycarbophil 976 (Noveon AA-1)	1.0%
2-Hydroxypropyl-β-cyclodextrin	20.0%
EDTA	0.1%
Hydrochloric Acid, 0.2 N	12.5%
Sodium Hydroxide, 2 N	to adjust pH
Water, q.s. to	100%

The cyclodextrin (20 g) is dissolved in approximately 60 g of sterile water for injection. The polymer is dispersed in the cyclodextrin solution, then the mixture is stirred for about 1 hour at 400 rpm. Then, 0.1 g of EDTA is added and stirred for 15 minutes. The mixture is autoclaved for 45 minutes at 121°C, then allowed to cool to room temperature. The aminosteroid (1 g) is dissolved in 12.5 g of 0.2 N aqueous hydrochloric acid. The aminosteroid solution is added to the cyclodextrin/polymer mixture by sterile filtration. The pH is adjusted to about 7.2 with 2 N aqueous sodium hydroxide solution, the final weight of the formulation is adjusted to 100 g sterile water by sterile filtration. The formulation is sealed under a blanket of filtered nitrogen. The

aminosteroid is extensively solubilized in the resultant composition, but about 25% of the steroid remained undissolved. The pH is physiological and the osmolality is slightly hypotonic.

The resultant composition is of particular interest for topical treatment of ophthalmic conditions. Use of about 30 g of 2-hydroxypropyl-β-cyclodextrin in the above procedure is expected to substantially completely solubilize the aminosteroid.

The foregoing example can be repeated, substituting or adding one or more other aminosteroid therapeutic agents selected from the C_{20} through C_{26} aminosteroids of the formula XI structure (especially those which exhibit antioxidant functions), and pharmaceutically acceptable salts, hydrates, or solvates thereof. One such agent is U-77372E. The structure of U-77372E, 21-[4-(4,6-bis-(2-pyridinyl)triazin-2-yl)-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione methanesulfonate, may be obtained from the description in Braughler et al, Biochemical Pharmacology 37:3856 (1988).

EXAMPLE 2

A 100 g batch of pharmaceutical composition may be prepared as described below:

INGREDIENT	CONCENTRATION
(5)-4-methyl-2-{methyl-[4-(2-methyl-imidazo[4,5-C]pyridin-1-ylmethyl)-benzene sulphonyl]-amino}pentanoic acid ethyl ether (BB-882)	0.3%
Polycarbophil (Noveon AA-1)	1.3%
2-Hydroxypropyl-β-cyclodextrin (HPBC)	15.0%
EDTA	0.1%
Hydrochloric Acid, 0.2 N	12.5%
Sodium Hydroxide, 2 N	to adjust pH
Water for injection q.s. to	100%

The HPBC (15 g) is dissolved in approximately 60 g of sterile water for injection. The polymer is dispersed in the HPBC solution, then the mixture is stirred for about 1 hour at 400 rpm. Then, 0.1 g of EDTA is added and stirred for 15 minutes. The mixture is autoclaved for 20 minutes at 121°C, then allowed to cool to room temperature. BB-882 is a PAF-antagonist useful as an antiinflamatory therapeutic agent. BB-882 (.3 g) is dissolved in 12.5 g of 0.2 N hydrochloric acid. The BB-882 solution is added to the HPBC/polymer mixture by sterile filtration while mixing. The pH is adjusted to about 6.0 with 2 N sodium hydroxide solution and the final weight of the formulation is adjusted to 100 g with sterile water by sterile filtration.

EXAMPLE 3

A 100 g batch of pharmaceutical composition may be prepared as described below:

INGREDIENT	CONCENTRATION
[4(N-hydroxyamino)-2R-isobutyl-3S-(thienyl-thiomethyl)-succinyl]-L-phenylalanine-N-methylamide (BB-94)	0.3%
Polycarbophil (Noveon AA-1)	1.3%
2-Hydroxypropyl-β-cyclodextrin (HPBC)	15.0%
EDTA	0.1%
Hydrochloric Acid, 0.2 N	12.5%
Sodium Hydroxide, 2 N	to adjust pH
Water for injection q.s. to	100%

The HPBC (15 g) is dissolved in approximately 60 g of sterile water for injection. The polymer is dispersed in the HPBC solution, then the mixture is stirred for about 1 hour at 400 rpm. Then, 0.1 g of EDTA is added and stirred for 15 minutes. The mixture is autoclaved for 20 minutes at 121°C, then allowed to cool to room temperature. BB-94 is a collogenase inhibitor. The BB-94 (.3 g) is dissolved in 12.5 g of 0.2 N hydrochloric acid. The aminosteroid solution is added to the HPBC/polymer mixture by sterile

filtration. The pH is adjusted to about 6.0 with 2 N sodium hydroxide solution. The final weight of the formulation is adjusted to 100 g with sterile water.

EXAMPLE 4

A 100 g batch of pharmaceutical composition may be prepared as described below:

INGREDIENT	CONCENTRATION
Levobunalol HCl	1.0%
Polycarbophil (Noveon AA-1)	1.3%
2-Hydroxypropyl-β-cyclodextrin (HPBC)	15.0%
EDTA	0.1%
Hydrochloric Acid, 0.2 N	12.5%
Sodium Hydroxide, 2 N	to adjust pH
Water for injection q.s. to	100%

The HPBC (15 g) is dissolved in approximately 60 g of sterile water for injection. The polymer is dispersed in the HPBC solution, then the mixture is stirred for about 1 hour at 400 rpm. Then, 0.1 g of EDTA is added and stirred for 15 minutes. The mixture is autoclaved for 45 minutes at 121°C, then allowed to cool to room temperature. Levobunolol HCl is an antiglaucoma therapeutic agent. The levobunolol HCl (1 g) is dissolved in 12.5 g of water of pH 7.2. The levobunolol HCl solution is added to the HPBC/polymer mixture by sterile filtration. The pH is adjusted to about 6.0 with 2 N sodium hydroxide solution by sterile filtration. The final weight of the formulation is adjusted to 100 g with sterile water by sterile filtration.

EXAMPLE 5

A 100 g batch of pharmaceutical composition is prepared as described below:

Ingredient	Concentration
L-Asparaginyl-L-Leucyl-Glycyl-L-Valyl-S-Acetamidomethyl-L-Cysteinamide Acetate (CBT-101)	1%
Polycarbophil (Noveon AA-1)	1%
Sodium Glycocholate	1%
2-Hydroxypropyl-β-cyclodextrin (HPBC)	4%
Sodium Chloride (NaCl)	0.34%
Disodium Acetate (EDTA)	0.1%
Sodium Hydroxide, 10 N.	to adjust pH
Water for injection, q.s. to	100%

The polymer is dispersed in approximately 60 g of sterile water for injection, stirred for 1 hour at 400 rpm. Then 0.1 g of EDTA is added and stirred for 15 minutes, 0.34 g of NaCl is added and stirred for 15 minutes, 1 g of sodium glycocholate is added to the mixture, and stirred for 15 minutes. The mixture is autoclaved for 45 minutes at 121°C, then allowed to cool to room temperature. Dissolve HPBC (4 g) in 15 g of sterile water for injection, then add 1 g of CBT-101 to the HPBC solution. Add the CBT-101/HPBC solution to the polymer mixture by sterile filtration. The pH is adjusted to about 7-0 with 10 N. sodium hydroxide solution by sterile filtration. The final weight of the formulation is adjusted to 100 g with sterile water by sterile filtration. CBT-101 is useful in treatment of glaucoma.

Although only preferred embodiments are specifically illustrated and described herein, it will be appreciated that many modifications and variations of the present invention are possible in light of the above teaching and within the purview of the appended claims without departing from the spirit and intended scope of the invention.

EXAMPLE 6

A 100 g batch of pharmaceutical composition may be prepared as described below:

INGREDIENT	CONCENTRATION (% w/w)
Aminosteroid U-74006F	1.0%
Carbopol 910	2.0%
2-Hydroxypropyl-β-cyclodextrin	20.0%
EDTA	0.1%
Hydrochloric Acid, 0.2 N	12.5%
Sodium Hydroxide, 2 N	to adjust pH
Water, q.s. to	100%

The cyclodextrin (20 g) is dissolved in approximately 60 g of sterile water for injection. The polymer is dispersed in the cyclodextrin solution, then the mixture is stirred for about 1 hour at 400 rpm. Then, 0.1 g of EDTA is added and stirred for 15 minutes. The mixture is autoclaved for 45 minutes at 121°C, then allowed to cool to room temperature. The aminosteroid (1 g) is dissolved in 12.5 g of 0.2 N aqueous hydrochloric acid. The aminosteroid solution is added to the cyclodextrin/polymer mixture by sterile filtration. The pH is adjusted to about 7.2 with 2 N aqueous sodium hydroxide solution, the final weight of the formulation is adjusted to 100 g sterile water by sterile filtration. The formulation is sealed under a blanket of filtered nitrogen.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a therapeutic agent, an effective stabilizing amount of carboxy-containing polymer and cyclodextrin, in an aqueous medium, wherein said cyclodextrin is selected from the group consisting of the hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α, β and γ-cyclodextrin, modified or nonmodified.

2. The composition of claim 1, wherein the cyclodextrin is present in an amount sufficient to at least partially solubilize said therapeutic agent, said amount being from about 1% to about 50% by weight, based on the total weight of the composition.

3. The composition of claim 2, wherein the cyclodextrin is present in an amount from about 1% to about 25% by weight, based on the total weight of the composition.

4. The composition of claim 2, wherein the polymer is about 0.1% to about 10% of the composition.

5. A composition of claim 2 wherein the polymer is lightly cross-linked and is about 0.1% to about 6.5% by weight of the composition.

6. The composition of claim 3, wherein the polymer is about 0.5% to about 2% of the composition.

7. The composition of claim 4, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin.

8. The composition of claim 4, wherein the therapeutic agent is selected from the group consisting of [4(N-hydroxyamino)-2R-isobutyl-3S-(thienyl-thiomethyl)-succinyl]-L-phenylalanine-N-methylamide,((5)-4-methyl-2-{methyl-[4-(2-methyl-imidazo[4,5-C]pyridin-1-ylmethyl)-benzene sulphonyl]-amino}pentanoic acid ethyl ether, fluoromethalone, prednisolone acetate, dexamethasone, erythromycin, hydrocortisone, CBT-101 and levobunolol HCl.

9. The composition of claim 7, wherein the therapeutic agent is selected from the group consisting of [4(N-hydroxyamino)-2R-isobutyl-3S-(thienyl-thiomethyl)-succinyl]-L-phenylalanine-N-methylamide,((5)-4-methyl-2-{methyl-[4-(2-methyl-imidazo[4,5-C]pyridin-1-ylmethyl)-benzene sulphonyl]-amino}pentanoic acid ethyl ether, fluoromethalone, prednisolone acetate, dexamethasone, erythromycin, hydrocortisone, CBT-101 and levobunolol.

10. The composition of claim 9, wherein the polymer is polycarbophil.

11. The composition of claim 8, wherein the polymer is CARBOPOL 974 P.

12. The composition of claim 7, further comprising one or more additives selected from the group consisting of sodium edetate, methyl paraben, propyl paraben, flavoring agents and colorants.

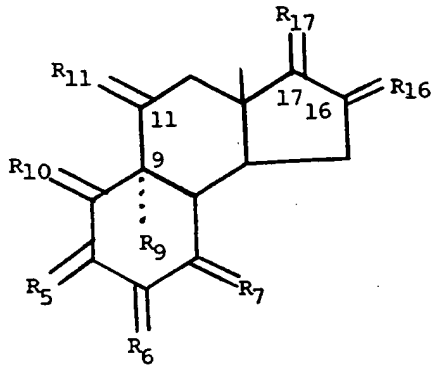
13. The composition of claim 4 wherein the composition in formulated for topical applications.

14. The composition of claim 13 formulated for topical ophthalmic application and having a viscosity of about 1,000 centipoises to about 100,000 centipoises and wherein said cyclodextrin is hydroxypropyl-β-cyclodextrin.

15. The composition of claim 14 and having a viscosity of about 1,000 centipoises to about 30,000 centipoises.

16. A composition of claim 14 having a pH between 3 and about 9 and an osmolality of about 10 mOsM to about 400 mOsM.

17. A pharmaceutical composition comprising an amino-substituted steroid therapeutic agent selected from the group consisting of the C_{20} through C_{26} aminosteroids of the formula XI



(XI)

where:

(A-I) R_6 is α-R_{61}:β-R_{62}, R_{10} is α-R_{101}:β-R_{102} and R_7 is α-H:β-H, where one of R_{61} and R_{62} is -H, and the other is -H, -F, or C_1-C_3 alkyl, R_{102} is $-CH_3$, R_{101} and R_5 taken together are $-(CH_2)_2-C(-R_{33})-CH=$ or -CH-CH-CO-CH=, where R_{33} is =O or α-H:β-OR_{34} or α-OR_{34}:β-H, where R_{34} is -H, $-P(=O)(OH)_2$, $-CO-CH_3$, $-CO-C_2H_5$, $-CO-C_6H_5$, $-CO-O-CH_3$ or $-CO-O-C_2H_5$;

(A-II) R_5 is α-R_{53}:β-R_{54}, R_6 is α-R_{63}:β-R_{64}, R_{10} is α-R_{103}:β-R_{104} and R_7 is α-H:β-H, where one of R_{63} and R_{64} is -H, and the other taken together with one of R_{53} and R_{54} forms a second bond between C_5 and C_6, R_{104} is $-CH_3$, R_{103} and the other of R_{53} and R_{54} taken together are $-(CH_2)_2$-C(H)(OH)-CH_2- or $-(CH_2)_2$-C[H][OP(=O)-$(OH)_2$]-CH_2-;

(A-III) R_{10} and R_5 taken together are =CH-CH=C(OR_3)-CH= where R_3 is -H, -P(=O)$(OH)_2$, C_1-C_3 alkyl, -CO-H, C_2-C_4 alkanoyl or benzyl, R_6 is α-R_{65}:β-R_{66} where one of R_{65} and R_{66} is -H, and the other is -H, -F, or C_1-C_3 alkyl and R_7 is α-H:β-H;

(A-IV) R_5 is α-R_{57}:β-R_{58}, R_6 is α-R_{67}:β-R_{68}, R_7 is α-H:β-H and R_{10} is α-R_{107}:β-R_{108}, where one of R_{57} and R_{58} is -H, R_{107} and the other of R_{57} and R_{58} taken together are $-(CH_2)_2$-C(=R_{33})-CH_2, where R_{33} is as defined above, R_{108} is $-CH_3$, where one of R_{67} and R_{68} is -H and the other is -H, -F, or C_1-C_3 alkyl;

(A-V) R_6 is R_{69}:R_{610}, R_7 is R_{79}:R_{710}, R_{10} is α-R_{109}:R_{1010}, where one of R_{69} and R_{610} is -H and the other taken together with one of R_{79} and R_{710} forms a second bond between C_6 and C_7, and the other of R_{79} and R_{710} is -H, R_{1010} is $-CH_3$, R_{109} and R_5 taken together are $-(CH_2)_2$-C(=R_{33})-CH= or -CH=CH-CO-CH=, where R_{33} is as defined above; where:

(C-I) R_{11} is α-R_{111}:β-R_{112}, where one of R_{111} and R_{112} is taken together with R_9 to form a second bond between C_9 and C_{11} and the other of R_{111} and R_{112} is -H;

(C-II) R_9 is -Cl and R_{11} is =O or α-H:β-R_{114} where R_{114} is -Cl or -OH;

(C-III) R_9 is -H or -F and R_{11} is =O or α-R_{115}:β-R_{116}, where one of R_{115} and R_{116} is -H, and the other of R_{115} and R_{116} is -H, -OH or C_1-C_{12} alkoxy;

(C-IV) R_9 is -H or -F and R_{11} is α-O-CO-R_{117}:β-H, where R_{117} is

(A) C_1-C_3 alkyl,

(B) C_1-C_{12} alkoxy,

(C) furanyl,

(D) -$NR_{122}R_{123}$, where one of R_{122} and R_{123} is -H, methyl or ethyl and the other is -H, C_1-C_4 alkyl or phenyl,

(E) -X_3-X_1, where X_3 is -O- or a valence bond, where X_1 is phenyl optionally substituted with 1 through 2 -Cl, -Br, C_1-C_3 alkoxy, -COOH, -NH_2, C_1-C_3 alkylamino, di(C_1-C_3)alkylamino, where the alkyl groups are the same or different, 1-pyrrolidinyl-, 1-piperidinyl, 1-hexamethylenimino-, 1-heptamethylenimino-, C_2-C_4 acylamino and -NH-CHO or with 1 -F or -CF_3;

where:

(D-I) R_{16} is R_{161}:R_{162} and R_{17} is R_{171}:R_{172}, where one of R_{161} and R_{162} is -H or -CH_3 and the other taken together with one of R_{171} and R_{172} forms a second bond between C_{16} and C_{17}, and the other of R_{171} and R_{172} is -C(=Z)-$(CH_2)_n$-$NR_{21}R_{210}$, where Z is =O, =CH_2 or R_{179}:-H where R_{179} is -H or -CH_3, where n is 0 through 6, where

(A) R_{21} is

(1) -$(CH_2)_m$-NR_{211}-X_2, where m is 2, 3 or 4, where R_{211} is -H or C_1-C_3 alkyl, where X_2 is: [A]

(a) pyridin-2-, 3- or 4-yl or the N-oxide thereof optionally substituted by 1 or 2 R_{212}, being the same or different, where R_{212} is

(i) -F,

(ii) -Cl,

(iii) -Br,

(iv) C_1-C_5 alkyl,

(v) -CH_2-CH=CH_2,

(vi) -X_1, where X_1 is as defined above,

(vii) $-NR_{213}R_{213}$ where the R_{213}'s are the same or different and are -H, C_1-C_3 alkyl or $-CH_2-CH=CH_2$,

(viiiα) $^*CH_2-(CH_2)_q-CH_2-N^*-$ where the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring, where q is 1 through 5,

(viiiβ) $^*CH_2-CH_2-(CH_2)_c-G-(CH_2)_d-CH_2-CH_2-N^*-$ where the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring, where G is -O-, -S-, -SO-, $-SO_2-$ or $-NHR_{214}$, where R_{214} is -H, C_1-C_3 alkyl, or X_1 as defined above, where c and d are the same or different and are 0 through 2 with the proviso that the total number of ring carbon atoms is 4, 5 or 6, [a]

(ix) 3-pyrrolin-1-yl, [b]

(x) pyrrol-1-yl optionally substituted with C_1-C_3 alkyl, [c]

(xi) piperidin-1-yl optionally substituted with 1 or 2 C_1-C_3 alkyl, [d]

(xii) 1,2,3,6-tetrahydro-pyridin-1-yl, [e]

(xiii) 1-hexamethyleneimino containing a 3- or 4- double bond or 3- and 5-double bonds, [f]

(xiv) 1,4-dihydro-1-pyridinyl substituted in the 4 position by two C_1-C_3 alkyl being the same or different, [g]

(xv) -OH,

(xvi) C_1-C_3 alkoxy,

(xvii) $-NR_{217}-(CH_2)_e-Q$ where Q is 2-pyridinyl where R_{217} is -H or C_1-C_3 alkyl and e is 0 through 3 (1)

(xviii) pyridin-2-, 3- or

4-yl,

(b) 1,3,5-triazin-4-yl or the N-oxide thereof optionally substituted at the 2- and/or 6- position with R_{212} as is defined above, (4)

(c) pyrimidin-4-yl or the N-oxide thereof optionally substituted at the 2- and/or 6- position with R_{212} as is defined above, (5)

(d) pyrimidin-2-yl optionally substituted at the 4- and/or 6- position with 1 or 2 R_{212} as is defined above, (6)

(e) pyrazin-2-yl optionally substituted with 1 or 2 R_{212} as is defined above, (7)

(f) imidazol-2-yl optionally substituted in the 1 position with C_1-C_3 alkyl or -X_1, where X_1 is as defined above, and further optionally substituted with 1 or 2 R_{212} as defined above, (8)

(g) 1,3,4-triazol-2-yl optionally substituted in the 1 position with C_1-C_3 alkyl or -X_1, where X_1 is as defined above, and further optionally substituted with R_{212} as defined above, (9)

(h) imidazol-4- or 5-yl optionally substituted in the 1 position with C_1-C_3 alkyl or -X_1, where X_1 is as defined above, and further optionally substituted with 1 or 2 R_{212} as defined above, (10)

(i) benzo[b]thien-2-yl, (12a)

(j) indol-2-yl, (12b)

(k) benzo[b]thiazol-2-yl, (12c)

(l) benzimidazol-2-yl, (12d)

(m) 4-[2-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]ethyl]piperazinyl, (13)

(n) 1,2,4-triazin-3-yl optionally

substituted at the 5- and/or 6- position with R_{212} as is defined above, (14)

(2) (1-piperazinyl)-(C_2-C_4)alkyl optionally substituted in the 4- position with -X_1 or -X_2 as defined above, [B]

(3) -X_2, as defined above, [O]

(4) -$(CH_2)_m$-X_4 where m is as defined above and where X_4 is

(a) -O-CH_2CH_2-Y, where Y is C_1-C_3 alkylamino, di(C_1-C_3)alkylamino where the alkyl groups are the same or different, C_3-C_6 alkyleneimino, optionally substituted with 1 or 2 C_1-C_3 alkyl,

(b) -$NR_{220}CH_2CH_2$-Y, where R_{220} is -H or C_1-C_3 alkyl and Y is as defined above,

(c) -$(CH_2)_g$-$N(R_{220})$-X_2, where g is 2, 3 or 4, and where R_{220} and X_2 are as defined above, [H]

(5) -$(CH_2)_m$-$NR_{222}R_{223}$, where R_{222} is -H or C_1-C_3 alkyl and R_{223} is -X_1 or -X_2 as defined above, or R_{222} and R_{223} are taken together with the attached nitrogen atom to form a saturated mono-nitrogen C_3-C_6 heterocyclic ring and where m is as defined above, [I]

(6) -$(CHCH_3)_b$-$(CH_2)_f$-R_{224}, where b is 0 and f is 1 through 3 or b is one and f is 0 through 3, where R_{224} is phenyl substituted with 1 through 3 -OH, C_1-C_3 alkoxy, -$NR_{225}R_{226}$ where R_{225} and R_{226} are the same or different and are -H, C_1-C_3 alkyl or are taken together with the attached nitrogen atom to form a C_4-C_7 cyclic amino ring, [J]

(7) -$(CH_2)_i$-X_2, where i is 1 through 4 and X_2 is as defined above, [K]

(8) (1-piperazinyl)acetyl substituted in the 4-position by X_2 where X_2 is as defined above, [L]

(9) (1-piperazinyl)carbonylmethyl substituted in the 4- position by -X_2 where X_2 is as defined above, and [M]

(B) R_{210} is

(1) -H,

(2) C_1-C_3 alkyl,

(3) C_5-C_7 cycloalkyl,

(4) $-(CH_2)_m-NR_{211}-X_2$, where m, R_{211} and X_2 are as defined above, [A]

(5) (1-piperazinyl)-(C_2-C_4)alkyl optionally substituted in the 4- position with $-X_1$ or $-X_2$ as defined above, [B]

(6) $-(CH_2)_m-X_4$, where m and X_4 are as defined above, [H]

(7) $-(CH_2)_m-NR_{222}R_{223}$, where m, R_{222} and R_{223} are as defined above, [I]

(8) $-(CHCH_3)_b-(CH_2)_f-R_{224}$, where b, f and R_{224} are as defined above, [J]

(C) R_{21} and R_{210} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of

(1) 2-(carboxy)-1-pyrrolidinyl optionally as the C_1-C_3 alkyl ester or as a pharmaceutically acceptable salt, [C-1]

(2) 2-(carboxy)-1-piperidinyl optionally as the C_1-C_3 alkyl ester or as a pharmaceutically acceptable salt, [C-2]

(3) 2-(carboxy)-1-hexamethyleneimino optionally as the C_1-C_3 alkyl ester or as a pharmaceutically acceptable salt, [C-3]

(4) 2-(carboxy)-1-heptamethylene-imino optionally as the C_1-C_3 alkyl ester or as a pharmaceutically acceptable salt, [C-4]

(5) 1-piperazinyl substituted in the 4- position with R_{228}-CO-$(CH_2)_j$- where R_{228} is $-X_1$, $-NR_{229}X_1$ or 2-furanyl,

where R_{229} is -H or C_1-C_3 alkyl, where j is 0 through 3 and X_1 is as defined above, [D]

(6) 1-piperazinyl substituted in the 4- position with X_2-$(CH_2)_j$-, where X_2 and j are as defined above, [E]

(7) 1-piperazinyl substituted in the 4- position with X_1-(CH_2)j-, where X_1 and j are as defined above, [F]

(8) 4-hydroxy-1-piperidinyl substituted in the 4- position with X_1 as defined above, [G]

(9) 1-piperazinyl substituted in the 4- position with X_2-NR_{229}-CO-$(CH_2)_i$-, where X_2, R_{229} and i are as defined above; [N]

(D-II) R_{16} is α-R_{163}:β-R_{164} where one of R_{163} and R_{164} is -H and the other is -H, -F, -CH_3 or -OH, and R_{17} is -CH-$(CH_2)_p$-$NR_{21}R_{210}$, where p is 1 or 2, where R_{21} and R_{210} are as defined above;

(D-III) R_{16} is α-R_{165}:β-R_{166} and R_{17} is α-R_{175}:β-R_{176}, where R_{165} is -H, -OH, -F or -CH_3 and R_{166} is -H, -OH, -F, or -CH_3, with the proviso that at least one of R_{165} and R_{166} is -H, where R_{175} is -H, -OH, -CH_3, -CH_2CH_3, C_2-C_7 alkanoyloxy or -O-CO-X_1, where X_1 is as defined above, and where R_{176} is -C(=Z)-(CH_2)n-$NR_{21}R_{210}$, where Z, n, R_{21} and R_{210} are as defined above;

(D-IV) the 16,17-acetonide of a compound where R_{165} is -OH, R_{166} is -H, R_{175} is -OH and R_{176} is -C(=Z)-$(CH_2)_n$-$NR_{21}R_{210}$, where Z, n, -R_{21} and R_{210} are as defined above;

and the pharmaceutically acceptable salts, hydrates and solvates thereof;

with the following overall provisos that:

(I) one of R_{161} or R_{162} is taken together with one of R_{171} or R_{172} to form a second bond between C_{16} and C_{17}, only when R_{10} is α-R_{101}:β-R_{102}, α-R_{103}:β-R_{104}, α-R_{107}:β-R_{108} or α-R_{109}:β-R_{1010},

(II) R_{17} is -CH-$(CH_2)_p$-$NR_{21}R_{210}$, only when R_{10} is α-R_{101}:β-R_{102}, a-R_{103}:β-R_{104}, α-R_{107}:β-R_{108} or α-R_{109}:β-R_{1010},

(III) R_5 and R_{10} taken together are =CH-CH=C(OR_3)-CH=, only when R_{17} is α-R_{175}:β-R_{176} or the 16,17-acetonide of a compound where R_{16} is α-OH:β-H and R_{17} is α-OH:β-C(=Z)-$(CH_2)_n$-$NR_{21}R_{210}$, and

(IV) R_5 is α-R_{57}:β-R_{58}, only when R_{17} is α-R_{175}:β-R_{176} or α-OH:β-C-(=Z)-$(CH_2)_n$-$NR_{21}R_{210}$, or the 16,17-acetonide thereof;

an effective stabilizing amount of lightly cross-linked carboxy-containing polymer and an amount of cyclodextrin sufficient to at least partially solubilize said therapeutic agent, in an aqueous medium, said cyclodextrin being selected from the group consisting of the hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α, β- and γ-cyclodextrin, modified or nonmodified.

18. The composition according to Claim 17, wherein the therapeutic agent is selected from the group consisting of the C_{21} aminosteroids of formula XI and the pharmaceutically acceptable salts, hydrates and solvates thereof.

19. The composition according to Claim 18, formulated for dermal administration.

20. The composition according to claim 18 formulated for topical ophthalmic administration.

21. The composition according to Claim 18, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin.

22. The composition according to Claim 17, wherein the cyclodextrin is present in an amount of from about 1% to about 50% by weight, based on the total weight of the composition.

23. The composition of claim 22 wherein the polymer is lightly cross-linked and is about 0.1% to about 6.5% by weight of the composition.

24. The composition according to Claim 18, wherein the cyclodextrin is present in an amount of from about 1% to about 25% by weight, based on the total weight of the composition.

25. The composition according to Claim 24, wherein the polymer is about 0.1% to about 6.5% by weight of the composition.

26. The composition according to Claim 24, wherein the polymer is about 0.5% to about 5% by weight of the composition.

27. A method for stabilizing and solubilizing a therapeutic agent in a pharmaceutical composition, comprising combining said therapeutic agent in an aqueous medium with an effective stabilizing amount of carboxy-containing polymer and an amount of cyclodextrin sufficient to at least partially solubilize said therapeutic agent, said cyclodextrin being selected from the group consisting of the hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α, β-and γ-cyclodextrin, modified or nonmodified.

28. The method of claim 27, wherein the cyclodextrin is present in an amount from about 1% to about 50% by weight, based on the total weight of the composition.

29. The method of claim 28, wherein the cyclodextrin is present in an amount from about 1% to about 25% by weight, based on the total weight of the composition.

30. The method of claim 28, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin.

31. The method of claim 30, wherein the polymer is about 0.1% to about 10% by weight of the composition.

32. The method of claim 28, wherein the polymer is lightly cross-linked and is about 0.1% to about 6.5% by weight of the composition.

33. The method of claim 31, wherein the polymer is about 0.5% to about 5% by weight of the composition.

34. The method of claim 29, wherein the therapeutic agent is selected from the group consisting of [4(N-hydroxyamino)-2R-isobutyl-3S-(thienyl-thiomethyl)-succinyl]-L-phenylalanine-N-methylamide,((5)-4-methyl-2-{methyl-[4-(2-methyl-imidazo[4,5-C]pyridin-1-ylmethyl)-benzene sulphonyl]-amino}pentanoic acid ethyl ether, fluoromethalone, prednisolone acetate, dexamethasone, erythromycin and hydrocortisone, CBT 101 and levobunolol HCl.

35. The method of claim 31, wherein the therapeutic agent is selected from the group consisting of [4(N-hydroxyamino)-2R-isobutyl-3S-(thienyl-thiomethyl)-succinyl]-L-phenylalanine-N-methylamide,((5)-4-methyl-2-{methyl-[4-(2-methyl-imidazo[4,5-C]pyridin-1-ylmethyl)-benzene sulphonyl]-amino}pentanoic acid ethyl ether, fluoromethalone, prednisolone acetate,

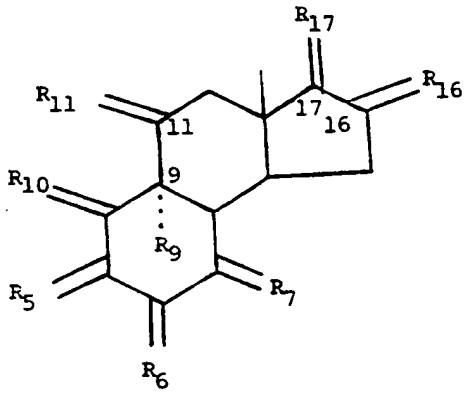
dexamethasone, erythromycin and hydrocortisone, CBT-101 and levobunolol HCl.

36. The method of claim 32, wherein the polymer is polycarbophil.

37. The method of claim 32, wherein the polymer is CARBOPOL 974 P.

38. The method of claim 29, further comprising one or more additives selected from the group consisting of sodium edetate, methyl paraben, propyl paraben, flavoring agents and colorants.

39. A method for stabilizing and solubilizing an amino-substituted steroid therapeutic agent in a pharmaceutical composition, said method comprising combining an amino-substituted steroid therapeutic agent selected from the group consisting of the C_{20} through C_{26} aminosteroids of the formula XI



(XI)

where:

(A-I) R_6 is α-R_{61}:β-R_{62}, R_{10} is α-R_{101}:β-R_{102} and R_7 is α-H:β-H, where one of R_{61} and R_{62} is -H, and the other is -H, -F, or C_1-C_3 alkyl, R_{102} is -CH_3, R_{101} and R_5 taken together are -$(CH_2)_2$-C(-R_{33})-CH= or -CH-CH-CO-CH=, where R_{33} is =O or α-H:β-OR_{34} or α-OR_{34}:β-H, where R_{34} is -H, -P(=O)$(OH)_2$, -CO-CH_3, -CO-C_2H_5, -CO-C_6H_5, -CO-O-CH_3 or -CO-O-C_2H_5;

(A-II) R_5 is α-R_{53}:β-R_{54}, R_6 is α-R_{63}:β-R_{64}, R_{10} is α-R_{103}:β-R_{104} and R_7 is α-H:β-H, where one of R_{63} and R_{64} is -H, and the other taken together with one of R_{53} and R_{54} forms a second bond between C_5 and C_6, R_{104} is -CH_3, R_{103} and the other of R_{53} and R_{54} taken together are -$(CH_2)_2$-C(H)(OH)-CH_2- or -$(CH_2)_2$-C[H][OP(=O)-$(OH)_2$]-CH_2-;

(A-III) R_{10} and R_5 taken together are =CH-CH=C(OR_3)-CH= where R_3 is -H, -P(=O)$(OH)_2$, C_1-C_3 alkyl, -CO-H, C_2-C_4 alkanoyl or benzyl, R_6 is α-R_{65}:β-R_{66} where one of R_{65} and R_{66} is -H, and the other is -H, -F, or C_1-C_3 alkyl and R_7 is α-H:β-H;

(A-IV) R_5 is α-R_{57}:β-R_{58}, R_6 is α-R_{67}:β-R_{68}, R_7 is α-H:β-H and R_{10} is α-R_{107}:β-R_{108}, where one of R_{57} and R_{58} is -H, R_{107} and the other of R_{57} and R_{58} taken together are -$(CH_2)_2$-C(=R_{33})-CH_2, where R_{33} is as defined above, R_{108} is -CH_3, where one of R_{67} and R_{68} is -H and the other is -H, -F, or C_1-C_3 alkyl;

(A-V) R_6 is R_{69}:R_{610}, R_7 is R_{79}:R_{710}, R_{10} is α-R_{109}:R_{1010}, where one of R_{69} and R_{610} is -H and the other taken together with one of R_{79} and R_{710} forms a second bond between C_6 and C_7, and the other of R_{79} and R_{710} is -H, R_{1010} is -CH_3, R_{109} and R_5 taken together are -$(CH_2)_2$-C(=R_{33})-CH= or -CH=CH-CO-CH=, where R_{33} is as defined above; where:

(C-I) R_{11} is α-R_{111}:β-R_{112}, where one of R_{111} and R_{112} is taken together with R_9 to form a second bond between C_9 and C_{11} and the other of R_{111} and R_{112} is -H;

(C-II) R_9 is -Cl and R_{11} is =O or α-H:β-R_{114} where R_{114} is -Cl

or -OH;

(C-III) R_9 is -H or -F and R_{11} is =O or α-R_{115}:β-R_{116}, where one of R_{115} and R_{116} is -H, and the other of R_{115} and R_{116} is -H, -OH or C_1-C_{12} alkoxy;

(C-IV) R_9 is -H or -F and R_{11} is α-O-CO-R_{117}:β-H, where R_{117} is

(A) C_1-C_3 alkyl,

(B) C_1-C_{12} alkoxy,

(C) furanyl,

(D) -$NR_{122}R_{123}$, where one of R_{122} and R_{123} is -H, methyl or ethyl and the other is -H, C_1-C_4 alkyl or phenyl,

(E) -X_3-X_1, where X_3 is -O- or a valence bond, where X_1 is phenyl optionally substituted with 1 through 2 -Cl, -Br, C_1-C_3 alkoxy, -COOH, -NH_2, C_1-C_3 alkylamino, di(C_1-C_3)alkylamino, where the alkyl groups are the same or different, 1-pyrrolidinyl-, 1-piperidinyl, 1-hexamethylenimino-, 1-heptamethylenimino-, C_2-C_4 acylamino and -NH-CHO or with 1 -F or -CF_3;

where:

(D-I) R_{16} is R_{161}:R_{162} and R_{17} is R_{171}:R_{172}, where one of R_{161} and R_{162} is -H or -CH_3 and the other taken together with one of R_{171} and R_{172} forms a second bond between C_{16} and C_{17}, and the other of R_{171} and R_{172} is -C(=Z)-$(CH_2)_n$-$NR_{21}R_{210}$, where Z is =O, =CH_2 or R_{179}:-H where R_{179} is -H or -CH_3, where n is 0 through 6, where

(A) R_{21} is

(1) -$(CH_2)_m$-NR_{211}-X_2, where m is 2, 3 or 4, where R_{211} is -H or C_1-C_3 alkyl, where X_2 is: [A]

(a) pyridin-2-, 3- or 4-yl or the N-oxide thereof optionally substituted by 1 or 2 R_{212}, being the same or different, where R_{212} is

(i) -F,

(ii) -Cl,

(iii) -Br,

(iv) C_1-C_5 alkyl,

(v) $-CH_2-CH=CH_2$,

(vi) $-X_1$, where X_1 is as defined above,

(vii) $-NR_{213}R_{213}$ where the R_{213}'s are the same or different and are -H, C_1-C_3 alkyl or $-CH_2-CH=CH_2$,

(viiiα) $^*CH_2-(CH_2)_q-CH_2-N^*-$ where the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring, where q is 1 through 5,

(viiiβ) $^*CH_2-CH_2-(CH_2)_c-G-(CH_2)_d-CH_2-CH_2-N^*-$ where the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring, where G is -O-, -S-, -SO-, $-SO_2-$ or $-NHR_{214}$, where R_{214} is -H, C_1-C_3 alkyl, or X_1 as defined above, where c and d are the same or different and are 0 through 2 with the proviso that the total number of ring carbon atoms is 4, 5 or 6, [a]

(ix) 3-pyrrolin-1-yl, [b]

(x) pyrrol-1-yl optionally substituted with C_1-C_3 alkyl, [c]

(xi) piperidin-1-yl optionally substituted with 1 or 2 C_1-C_3 alkyl, [d]

(xii) 1,2,3,6-tetrahydro-pyridin-1-yl, [e]

(xiii) 1-hexamethyleneimino containing a 3- or 4- double bond or 3- and 5-double bonds, [f]

(xiv) 1,4-dihydro-1-pyridinyl substituted in the 4 position by two C_1-C_3 alkyl being the same or

different, [g]

(xv) -OH,

(xvi) C_1-C_3 alkoxy,

(xvii) $-NR_{217}-(CH_2)_e-Q$ where Q is 2-pyridinyl where R_{217} is -H or C_1-C_3 alkyl and e is 0 through 3 (1)

(xviii) pyridin-2-, 3- or 4-yl,

(b) 1,3,5-triazin-4-yl or the N-oxide thereof optionally substituted at the 2- and/or 6- position with R_{212} as is defined above, (4)

(c) pyrimidin-4-yl or the N-oxide thereof optionally substituted at the 2- and/or 6- position with R_{212} as is defined above, (5)

(d) pyrimidin-2-yl optionally substituted at the 4- and/or 6- position with 1 or 2 R_{212} as is defined above, (6)

(e) pyrazin-2-yl optionally substituted with 1 or 2 R_{212} as is defined above, (7)

(f) imidazol-2-yl optionally substituted in the 1 position with C_1-C_3 alkyl or $-X_1$, where X_1 is as defined above, and further optionally substituted with 1 or 2 R_{212} as defined above, (8)

(g) 1,3,4-triazol-2-yl optionally substituted in the 1 position with C_1-C_3 alkyl or $-X_1$, where X_1 is as defined above, and further optionally substituted with R_{212} as defined above, (9)

(h) imidazol-4- or 5-yl optionally substituted in the 1 position with C_1-C_3 alkyl or $-X_1$, where X_1 is as defined above, and further optionally substituted with 1 or 2 R_{212} as defined above, (10)

(i) benzo[b]thien-2-yl, (12a)

(j) indol-2-yl, (12b)

(k) benzo[b]thiazol-2-yl, (12c)

(l) benzimidazol-2-yl, (12d)

(m) 4-[2-[4-[2,6-bis(1-pyrrolidinyl)-4-pyrimidinyl]-1-piperazinyl]ethyl]piperazinyl; (13)

(n) 1,2,4-triazin-3-yl optionally substituted at the 5- and/or 6- position with R_{212} as is defined above, (14)

(2) (1-piperazinyl)-(C_2-C_4)alkyl optionally substituted in the 4- position with $-X_1$ or $-X_2$ as defined above, [B]

(3) $-X_2$, as defined above, [O]

(4) $-(CH_2)_m-X_4$ where m is as defined above and where X_4 is

(a) $-O-CH_2CH_2-Y$, where Y is C_1-C_3 alkylamino, di(C_1-C_3)alkylamino where the alkyl groups are the same or different, C_3-C_6 alkyleneimino, optionally substituted with 1 or 2 C_1-C_3 alkyl,

(b) $-NR_{220}CH_2CH_2-Y$, where R_{220} is -H or C_1-C_3 alkyl and Y is as defined above,

(c) $-(CH_2)_g-N(R_{220})-X_2$, where g is 2, 3 or 4, and where R_{220} and X_2 are as defined above, [H]

(5) $-(CH_2)_m-NR_{222}R_{223}$, where R_{222} is -H or C_1-C_3 alkyl and R_{223} is $-X_1$ or $-X_2$ as defined above, or R_{222} and R_{223} are taken together with the attached nitrogen atom to form a saturated mono-nitrogen C_3-C_6 heterocyclic ring and where m is as defined above, [I]

(6) $-(CHCH_3)_b-(CH_2)_f-R_{224}$, where b is 0 and f is 1 through 3 or b is one and f is 0 through 3, where R_{224} is phenyl substituted with 1 through 3 -OH, C_1-C_3 alkoxy, $-NR_{225}R_{226}$ where R_{225} and R_{226} are the same or different and are -H, C_1-C_3 alkyl or are taken together with the attached nitrogen atom to form a C_4-C_7 cyclic amino ring, [J]

(7) $-(CH_2)_i-X_2$, where i is 1 through 4 and X_2 is as defined above, [K]

(8) (1-piperazinyl)acetyl substituted in the 4-position by X_2 where X_2 is as defined above, [L]

(9) (1-piperazinyl)carbonylmethyl substituted in the 4- position by $-X_2$ where X_2 is as defined above, and [M]

(B) R_{210} is

(1) -H,

(2) C_1-C_3 alkyl,

(3) C_5-C_7 cycloalkyl,

(4) $-(CH_2)_m-NR_{211}-X_2$, where m, R_{211} and X_2 are as defined above, [A]

(5) (1-piperazinyl)-(C_2-C_4)alkyl optionally substituted in the 4- position with $-X_1$ or $-X_2$ as defined above, [B]

(6) $-(CH_2)_m-X_4$, where m and X_4 are as defined above, [H]

(7) $-(CH_2)_m-NR_{222}R_{223}$, where m, R_{222} and R_{223} are as defined above, [I]

(8) $-(CHCH_3)_b-(CH_2)_f-R_{224}$, where b, f and R_{224} are as defined above, [J]

(C) R_{21} and R_{210} are taken together with the attached nitrogen atom to form a heterocyclic ring selected from the group consisting of

(1) 2-(carboxy)-1-pyrrolidinyl optionally as the C_1-C_3 alkyl ester or as a pharmaceutically acceptable salt, [C-1]

(2) 2-(carboxy)-1-piperidinyl optionally as the C_1-C_3 alkyl ester or as a pharmaceutically acceptable salt, [C-2]

(3) 2-(carboxy)-1-hexamethyleneimino optionally as the C_1-C_3 alkyl ester or as a pharmaceutically acceptable

salt, [C-3]

(4) 2-(carboxy)-1-heptamethylene-imino optionally as the C_1-C_3 alkyl ester or as a pharmaceutically acceptable salt, [C-4]

(5) 1-piperazinyl substituted in the 4- position with R_{228}-CO-$(CH_2)_j$- where R_{228} is -X_1, -$NR_{229}X_1$ or 2-furanyl, where R_{229} is -H or C_1-C_3 alkyl, where j is 0 through 3 and X_1 is as defined above, [D]

(6) 1-piperazinyl substituted in the 4- position with X_2-$(CH_2)_j$-, where X_2 and j are as defined above, [E]

(7) 1-piperazinyl substituted in the 4- position with X_1-(CH_2)j-, where X_1 and j are as defined above, [F]

(8) 4-hydroxy-1-piperidinyl substituted in the 4- position with X_1 as defined above, [G]

(9) 1-piperazinyl substituted in the 4- position with X_2-NR_{229}-CO-$(CH_2)_i$-, where X_2, R_{229} and i are as defined above; [N]

(D-II) R_{16} is α-R_{163}:β-R_{164} where one of R_{163} and R_{164} is -H and the other is -H, -F, -CH_3 or -OH, and R_{17} is -CH-$(CH_2)_p$-$NR_{21}R_{210}$, where p is 1 or 2, where R_{21} and R_{210} are as defined above;

(D-III) R_{16} is α-R_{165}:β-R_{166} and R_{17} is α-R_{175}:β-R_{176}, where R_{165} is -H, -OH, -F or -CH_3 and R_{166} is -H, -OH, -F, or -CH_3, with the proviso that at least one of R_{165} and R_{166} is -H, where R_{175} is -H, -OH, -CH_3, -CH_2CH_3, C_2-C_7 alkanoyloxy or -O-CO-X_1, where X_1 is as defined above, and where R_{176} is -C(=Z)-(CH_2)n-$NR_{21}R_{210}$, where Z, n, R_{21} and R_{210} are as defined above;

(D-IV) the 16,17-acetonide of a compound where R_{165} is -OH, R_{166} is -H, R_{175} is -OH and R_{176} is -C(=Z)-$(CH_2)_n$-$NR_{21}R_{210}$, where Z, n, -R_{21} and R_{210} are as defined above;

and the pharmaceutically acceptable salts, hydrates and solvates thereof;

with the following overall provisos that:

(I) one of R_{161} or R_{162} is taken together with one of R_{171} or R_{172} to form a second bond between C_{16} and C_{17}, only when R_{10} is α-R_{101}:β-R_{102}, α-R_{103}:β-R_{104}, α-R_{107}:β-R_{108} or α-R_{109}:β-R_{1010},

(II) R_{17} is -CH-$(CH_2)_p$-$NR_{21}R_{210}$, only when R_{10} is α-R_{101}:β-R_{102}, a-R_{103}:β-R_{104}, α-R_{107}:β-R_{108} or α-R_{109}:β-R_{1010},

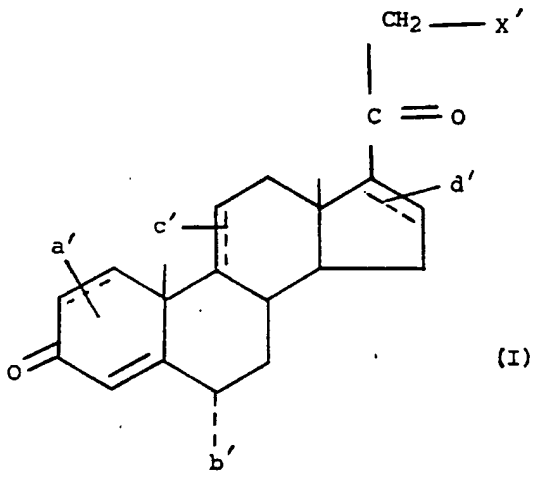
(III) R_5 and R_{10} taken together are =CH-CH=C(OR_3)-CH=, only when R_{17} is α-R_{175}:β-R_{176} or the 16,17-acetonide of a compound where R_{16} is α-OH:β-H and R_{17} is α-OH:β-C(=Z)-$(CH_2)_n$-$NR_{21}R_{210}$, and

(IV) R_5 is α-R_{57}:β-R_{58}, only when R_{17} is α-R_{175}:β-R_{176} or α-OH:β-C-(=Z)-$(CH_2)_n$-$NR_{21}R_{210}$, or the 16,17-acetonide thereof;

in an aqueous medium with an effective stabilizing amount of lightly cross-linked carboxy-containing polymer and an amount of cyclodextrin sufficient to at least partially solubilize said therapeutic agent, said cyclodextrin being selected from the group consisting of the hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of α, β- and γ-cyclodextrin, modified or nonmodified.

40. The method according to claim 39, wherein the therapeutic agent is selected from the group consisting of the C_{21} aminosteroids of formula XI and the pharmaceutically acceptable salts, hydrates and solvates thereof.

41. The method according to claim 34, wherein the therapeutic agent is selected from the group consisting of the C_{21} aminosteroids of the formula I



(I)

where:

a′ is selected from the group 1,2-dihydro (saturated) and 1,2-dehydro (1,2-double bond);

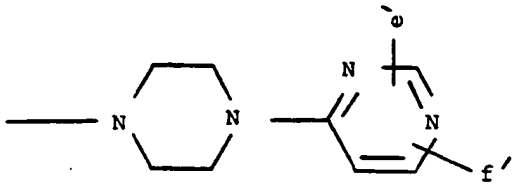
b′ is selected from the group 6α-H, 6α-methyl and 6α-flouro;

c′ is selected from the group 9,11-dihydro (saturated), 9(11)-dehydro (double bond), 9α-H-11α-OH-11β-H,9α-H-11β-OH-11α-H,9α-H-11-keto,9α-F-11β-OH-11α-H and 9α-F-11-keto;

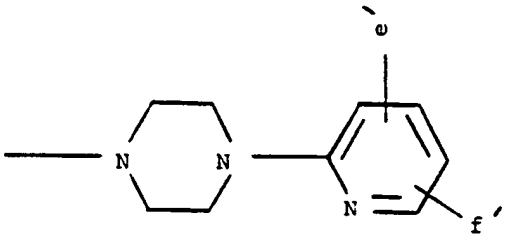
d′ is selected from the group 16α-methyl-16β-H-17α-H, 16β-methyl-16α-H-17α-H, 16-H_2-17α-H, 16-H-16,17-dehydro (double bond), and 16-methyl-16,17-dehydro. Less preferably, a 17α-OH group can be present instead of 17α-H when d′ is not 16-H-16,17-dehydro or 16-methyl-16,17-dehydro; and where:

X′ is selected from the complex 21-amino substituents X1′ and X2′ where

X1′ is



and

X2′ is 

where e′ and f′ may be the same or different and are selected from the group: H,NHR1′ and NR1′R2′, where R1′ and R2′ are C1 to C3 lower alkyl or R1′ and R2′, taken together with N, constitute a heterocyclic ring; and the pharmaceutically acceptable salts, hydrates and solvates thereof.

42. The method according to claim 41, wherein e′ and f′, which may be the same or different, are selected from the group consisting of H,NHR1′ and NR1′R2′, wherein R1′ and R2′ are C1 to C3 lower alkyl or R1′ and R2′, taken together with N, constitute a heterocyclic ring selected from the group consisting of 1-ethyleneimino, 1-trimethyleneimino, 1-pyrrolidinyl, 1-piperidinyl, 1-morpholinyl and 1-(4-methyl)piperazinyl.

43. The method according to claim 39, wherein the therapeutic agent is selected from the group consisting of 21-[4-(2,6-dipyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione or a pharmaceutically acceptable slat, hydrate or solvate thereof; 21-[4-[5,6-bis(diethylamino)-2-pyridinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione, or a pharmaceutically acceptable salt, hydrate or solvate thereof; and 21-[4-(3-ethylamino-2-pyridinyl)-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione,or a pharmaceutically acceptable salt, hydrate or solvate thereof.

44. The method according to claim 39, wherein the therapeutic agent is selected from the group consisting of the methanesulfonate salt of 21-[4-(2,6-dipyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione; the hydrochloride salt of 21-[4-[5,6-bis(diethylamino)-2-pyridinyl]-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione; and the hydrochloride or maleic acid salt of 21-[4-(3-ethylamino-2-pyridinyl)-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione.

45. The method according to claim 39, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin.

46. The method according to claim 39, wherein the cyclodextrin is used in an amount of from about 1% to about 50% by weight, based on the total weight of the composition.

47. The method of claim 46 wherein the polymer is lightly cross-linked and is about 0.1% to about 6.5% by weight of the composition.

48. The method according to claim 42, wherein the cyclodextrin is used in an amount of from about 1% to about 25% by weight, based on the total weight of the composition.

49. A method as recited in claim 43, wherein the polymer is about .5% to about 2% by weight of the composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/11651

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 47/28, 31/59, 37/22, 47/36, 31/70
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/ 78.04, 427, 428, 450; 514/169, 170, 172, 176, 774, 777, 781, 784, 785, 801, 912, 944

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,983,586 (BODOR) 08 JANUARY 1991, See entire document.	1-49
A	US, A, 4,383,992 (LIPARI) 17 MAY 1983, See entire document.	1-49

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 13 JANUARY 1993	Date of mailing of the international search report 16 FEB 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer CARLOS AZPURU Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

Intern...ional application No.
PCT/US93/11651

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/427, 428, 450; 514/169, 170, 172, 176, 774, 777, 781, 784, 785, 801, 912, 944